Choosing what to do, dopamine, and Parkinson's disease

Dr. James Surmeier
j-surmeier@northwestern.edu

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The first part is about the part of the brain that helps us to choose what to do...

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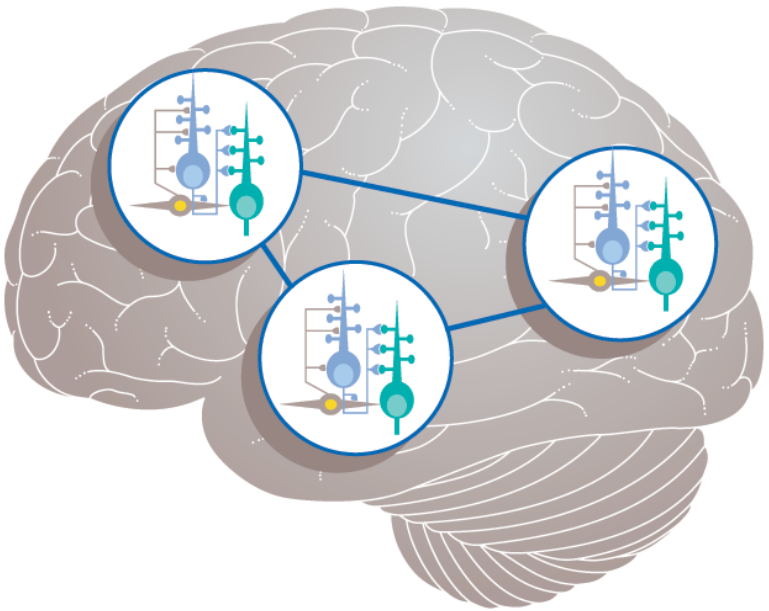
The second part is about what happens when this part of the brain becomes dysfunctional in Parkinson's disease...

The brain can be studied at several levels...

Networks



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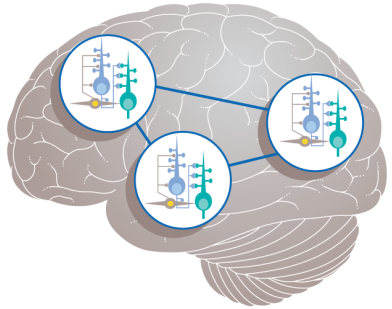
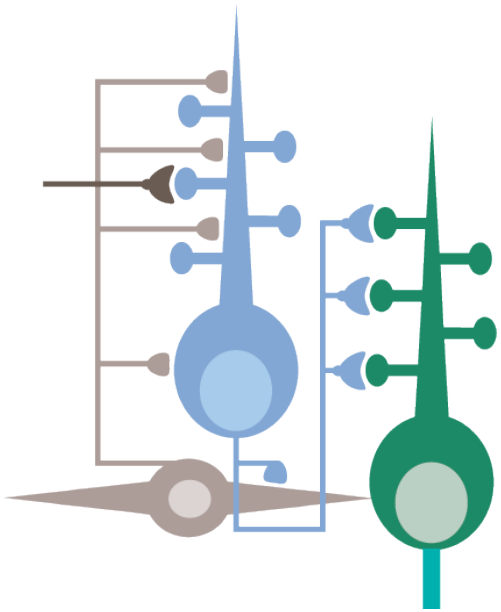


Circuits



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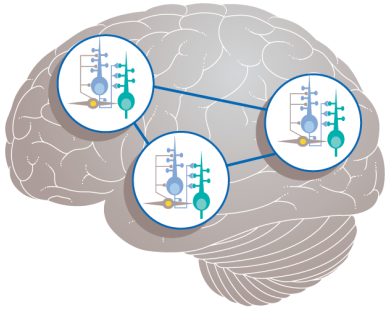

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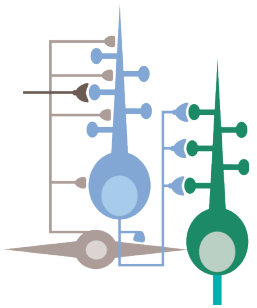
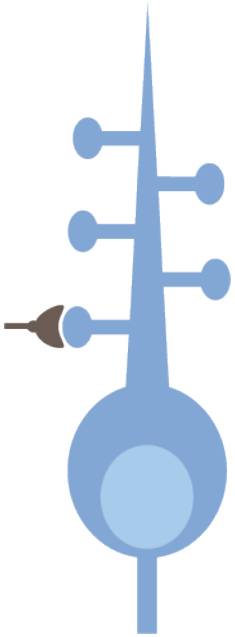


Neurons



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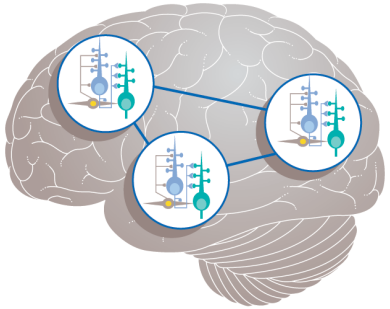

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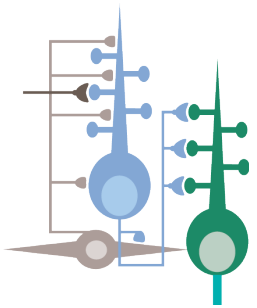
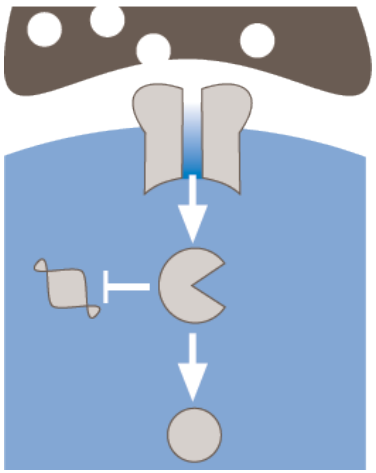


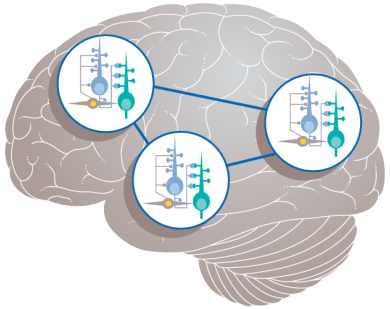
Neurons

Molecules



The talk today will span all these levels...

Networks



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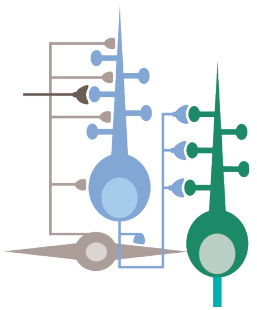

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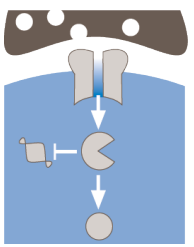
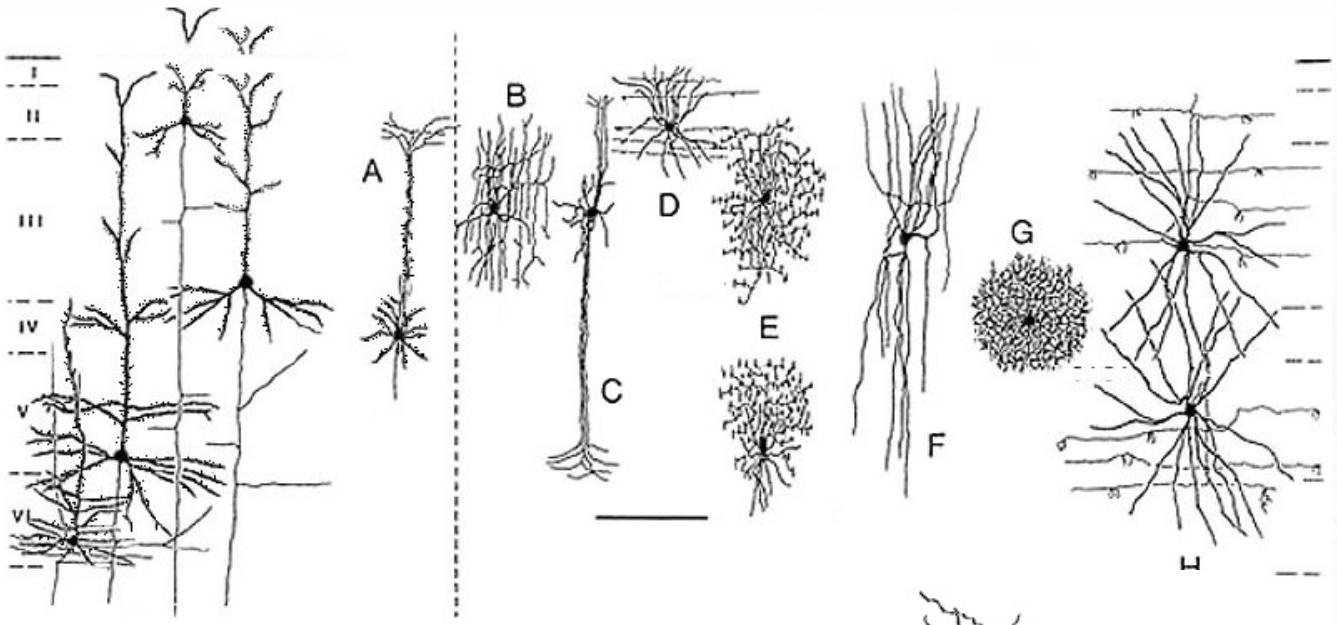
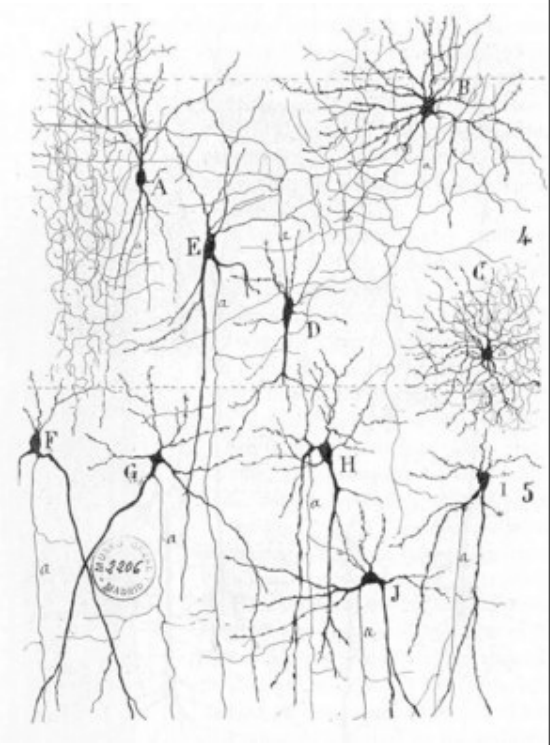
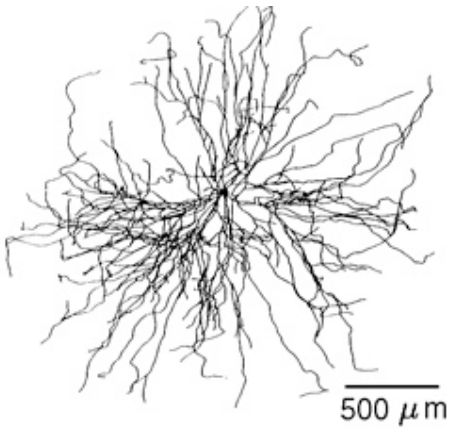
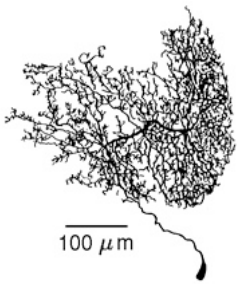


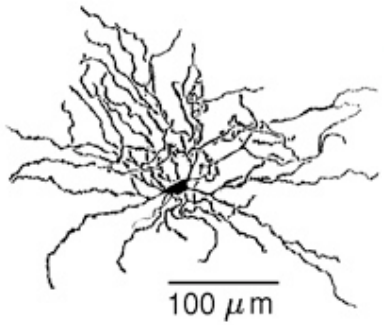
Neurons are the building blocks of the brain. They come in lots of shapes and sizes





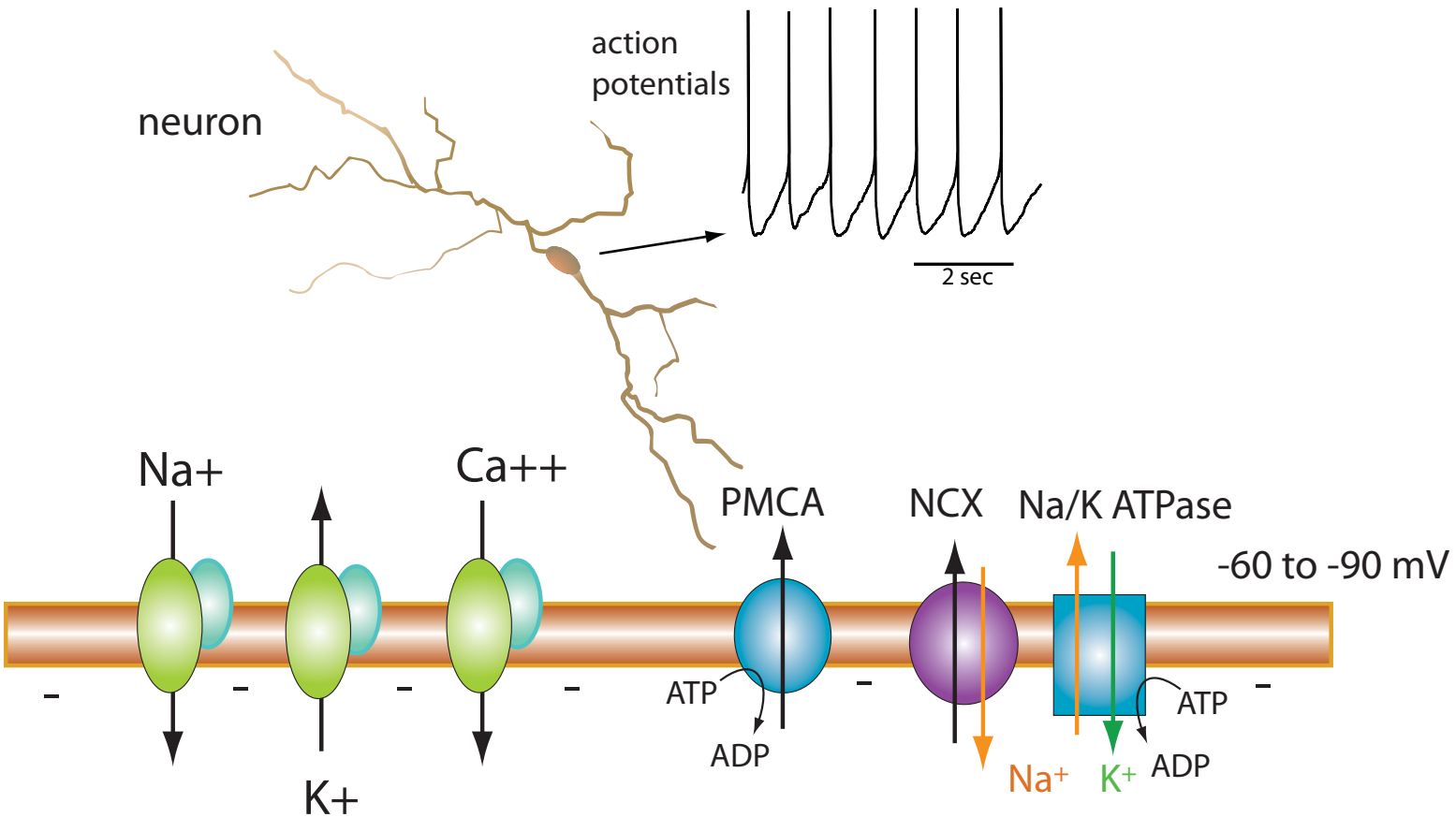




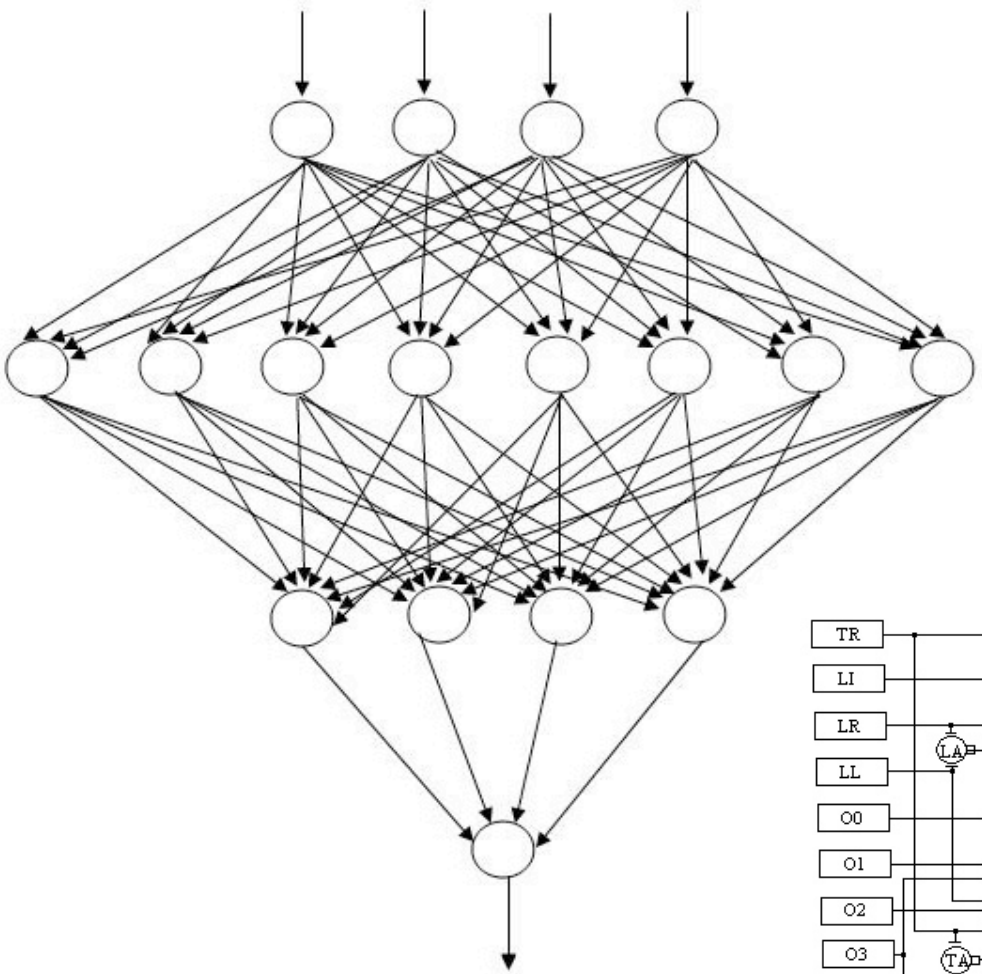


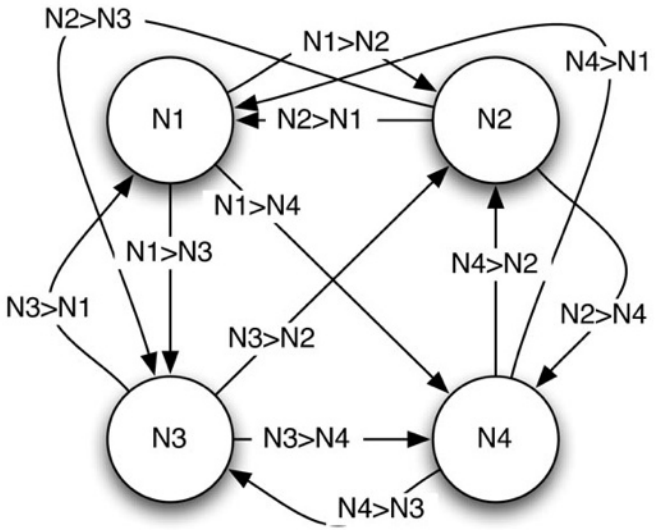
Neurons are electrochemical entities that communicate with one another through chemical signals...

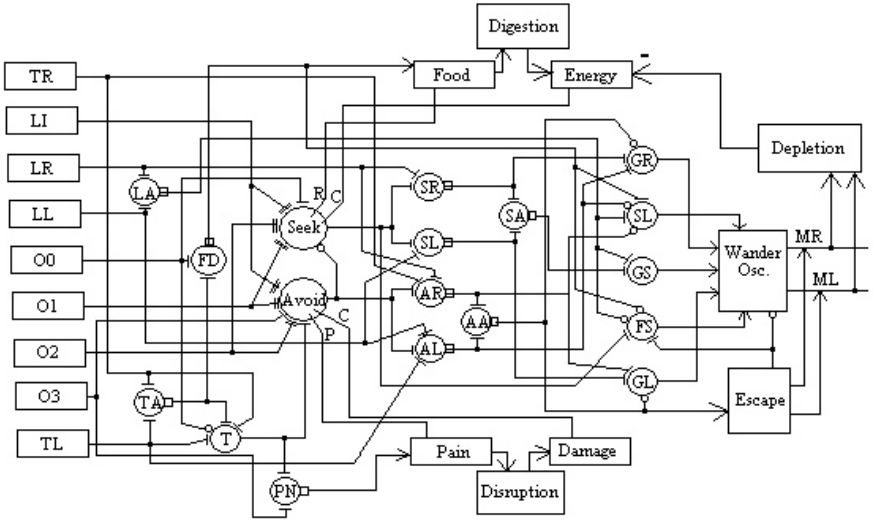
The computations performed by neurons rely upon electrochemical gradients across their membranes that a maintained by energy dependent pumps...



Neurons can be arranged in a variety of circuits that perform different functions...







At synapses, the release of fast transmitters produce excitatory or inhibitory changes in membrane potential

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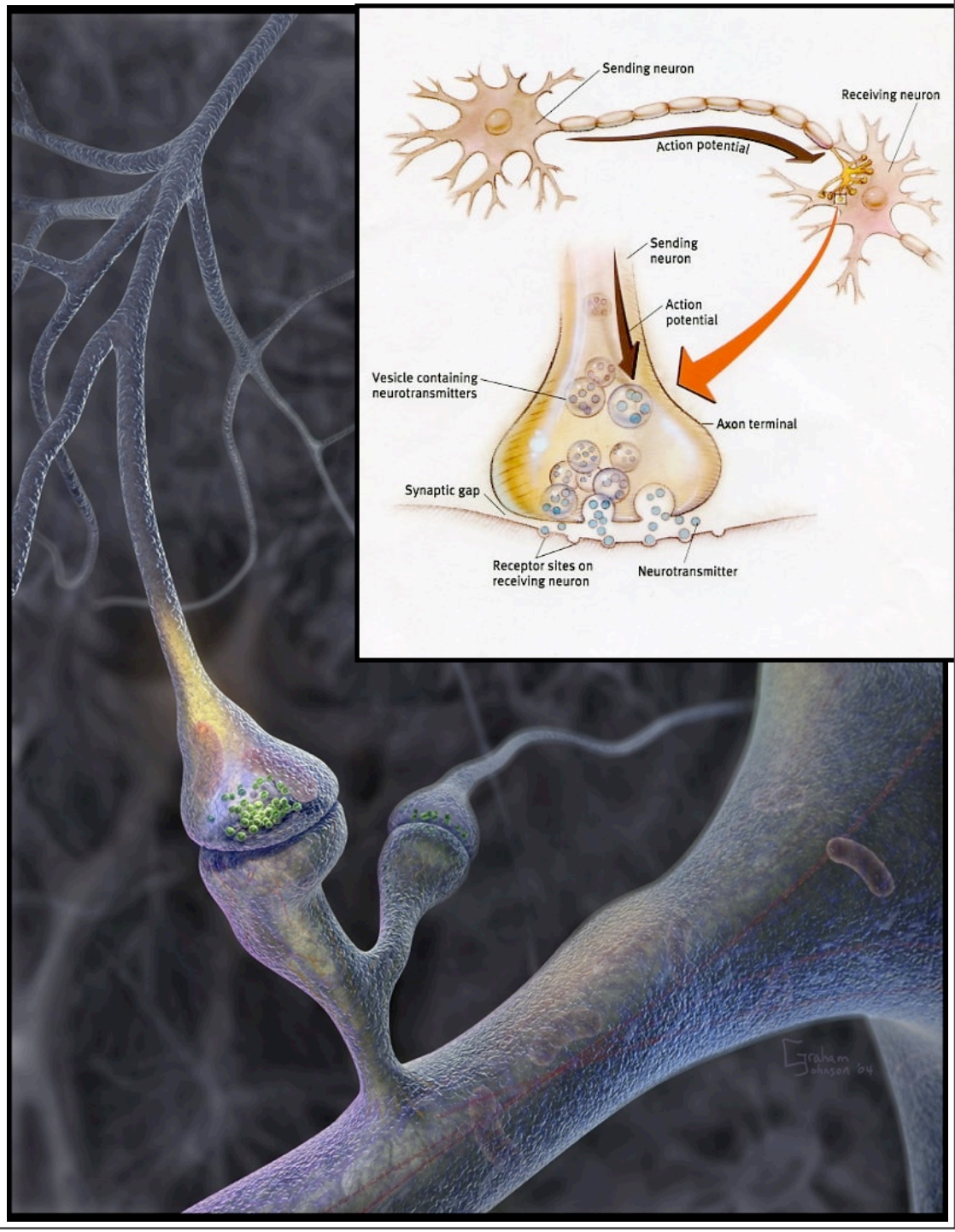

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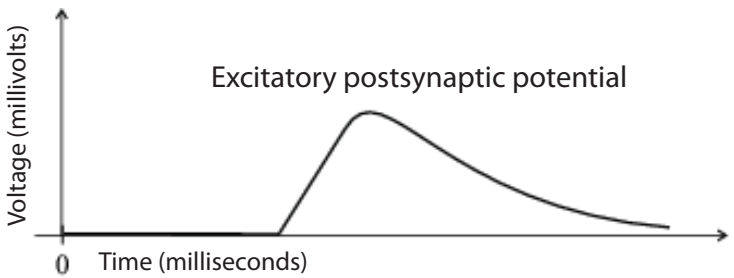

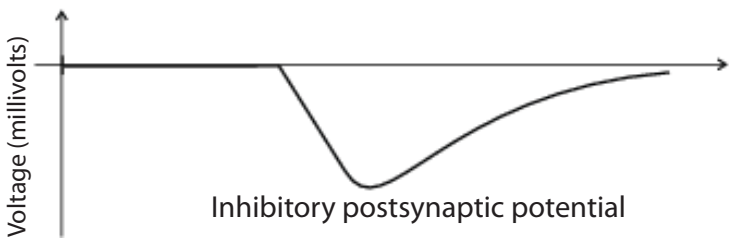

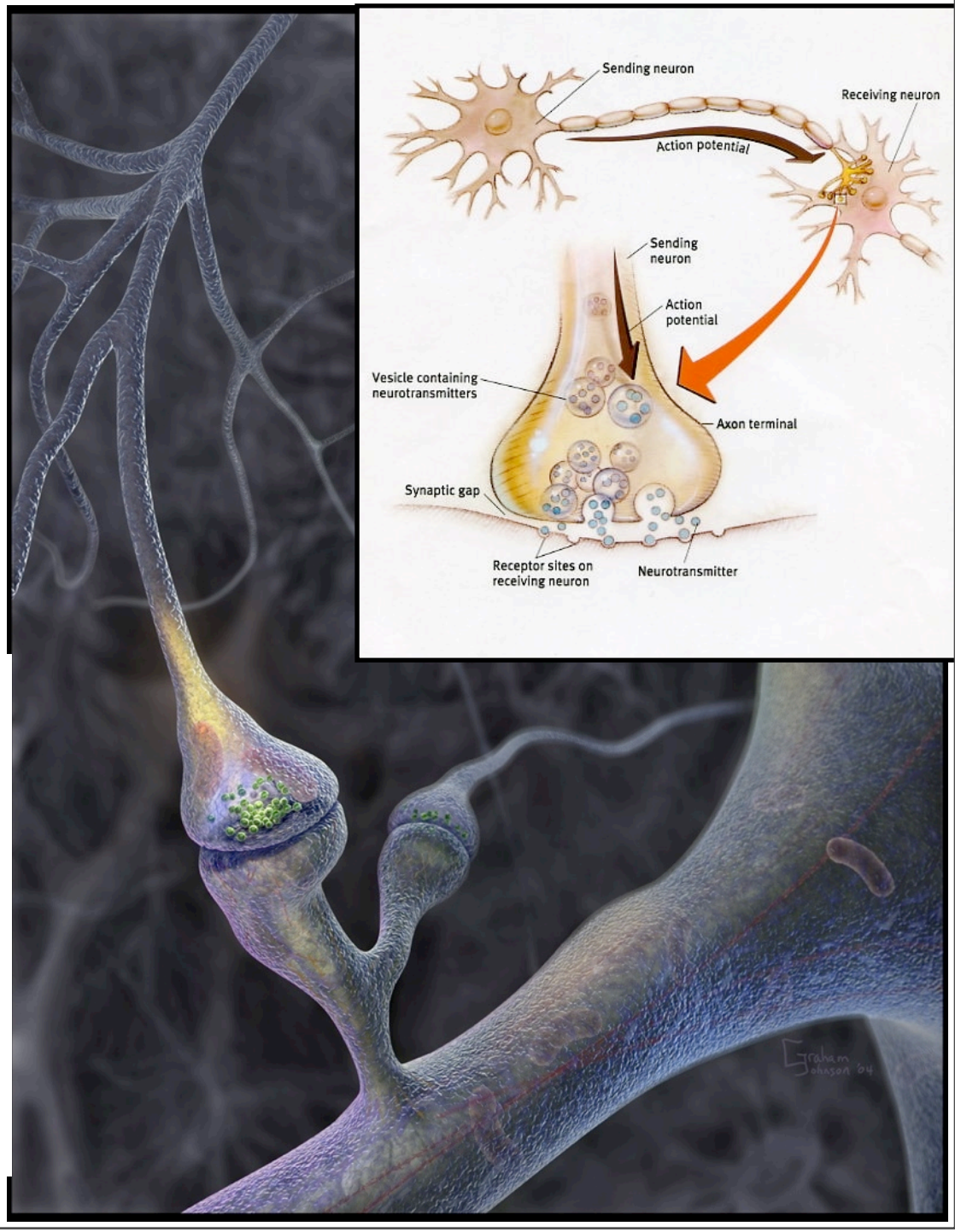

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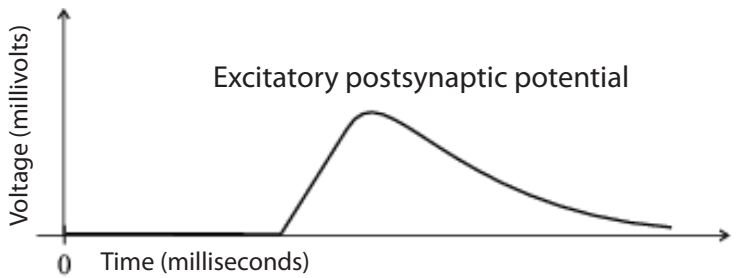
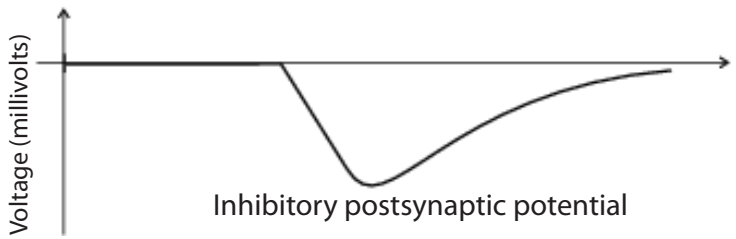
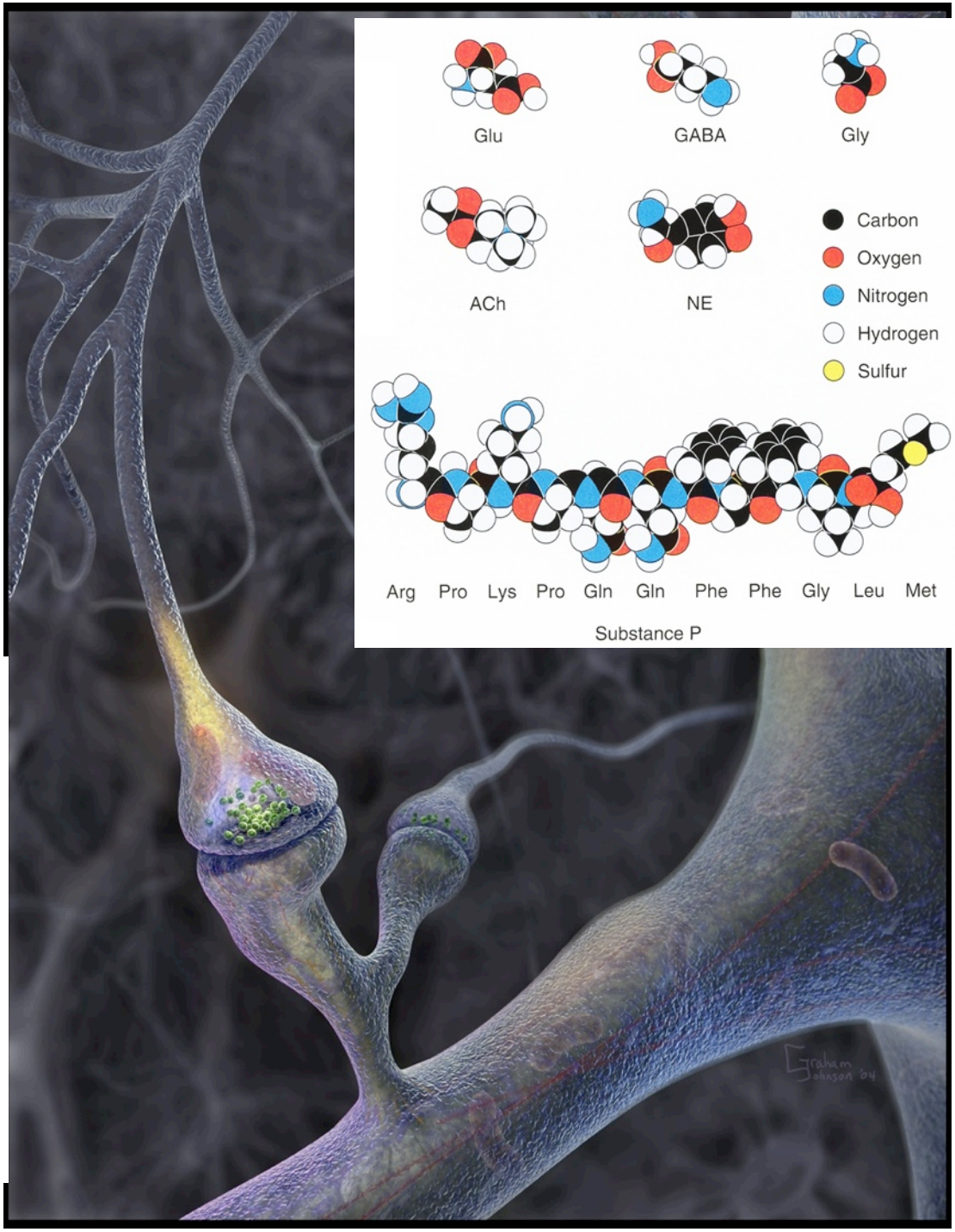
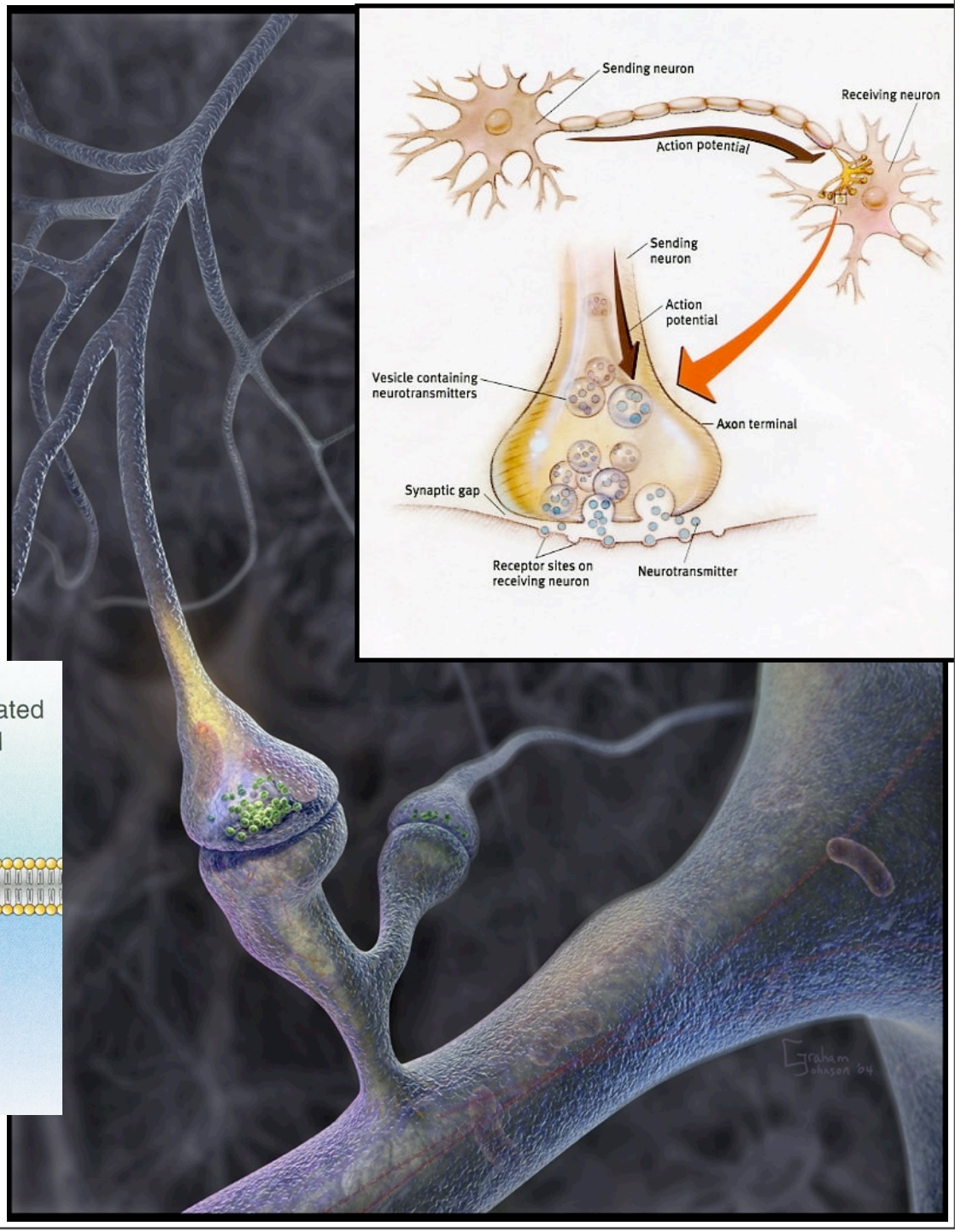
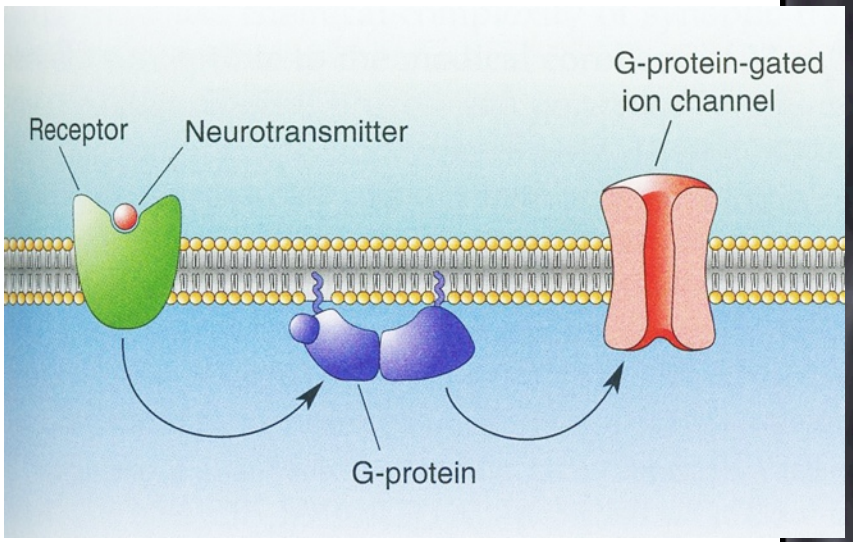






In addition to fast transmitters, neurons can release slow, neuromodulatory transmitters that produce alterations in neuronal structure and function





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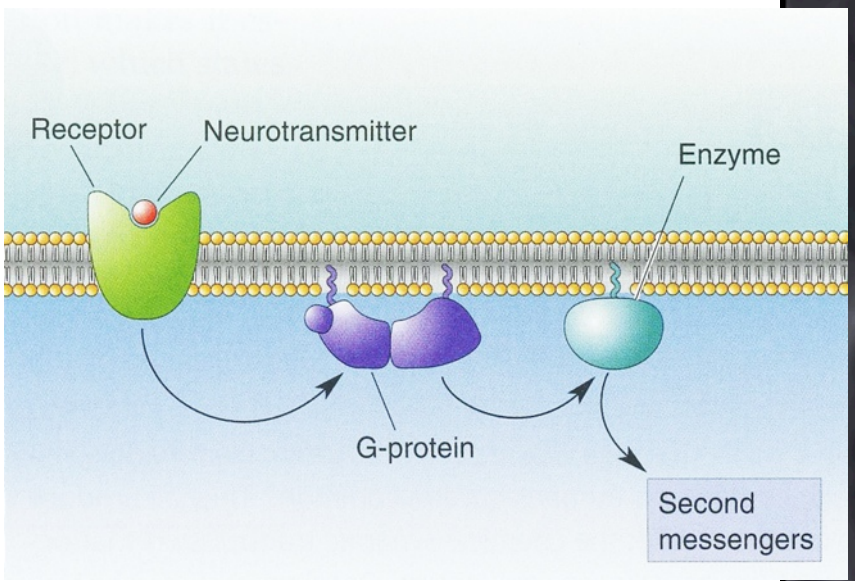
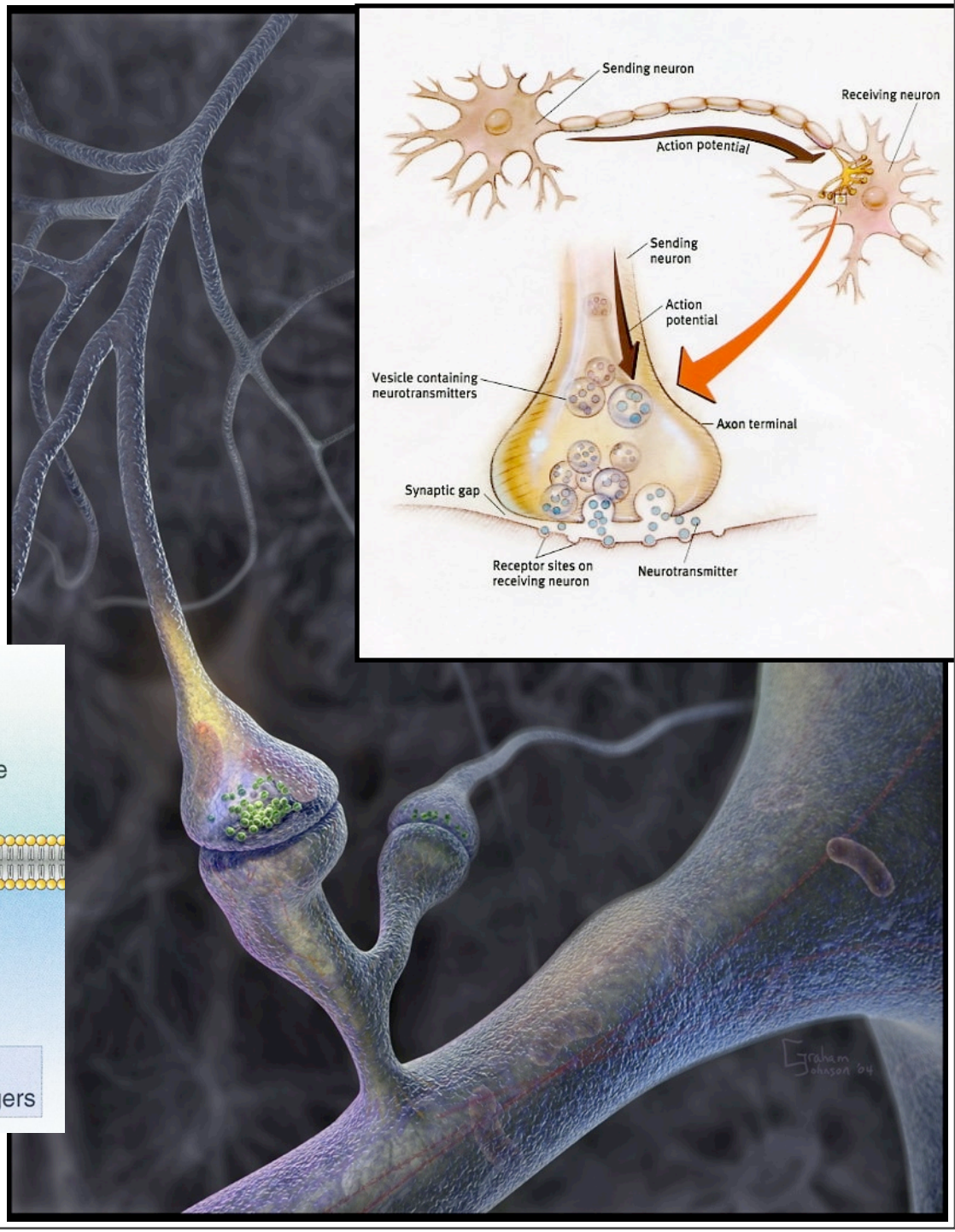
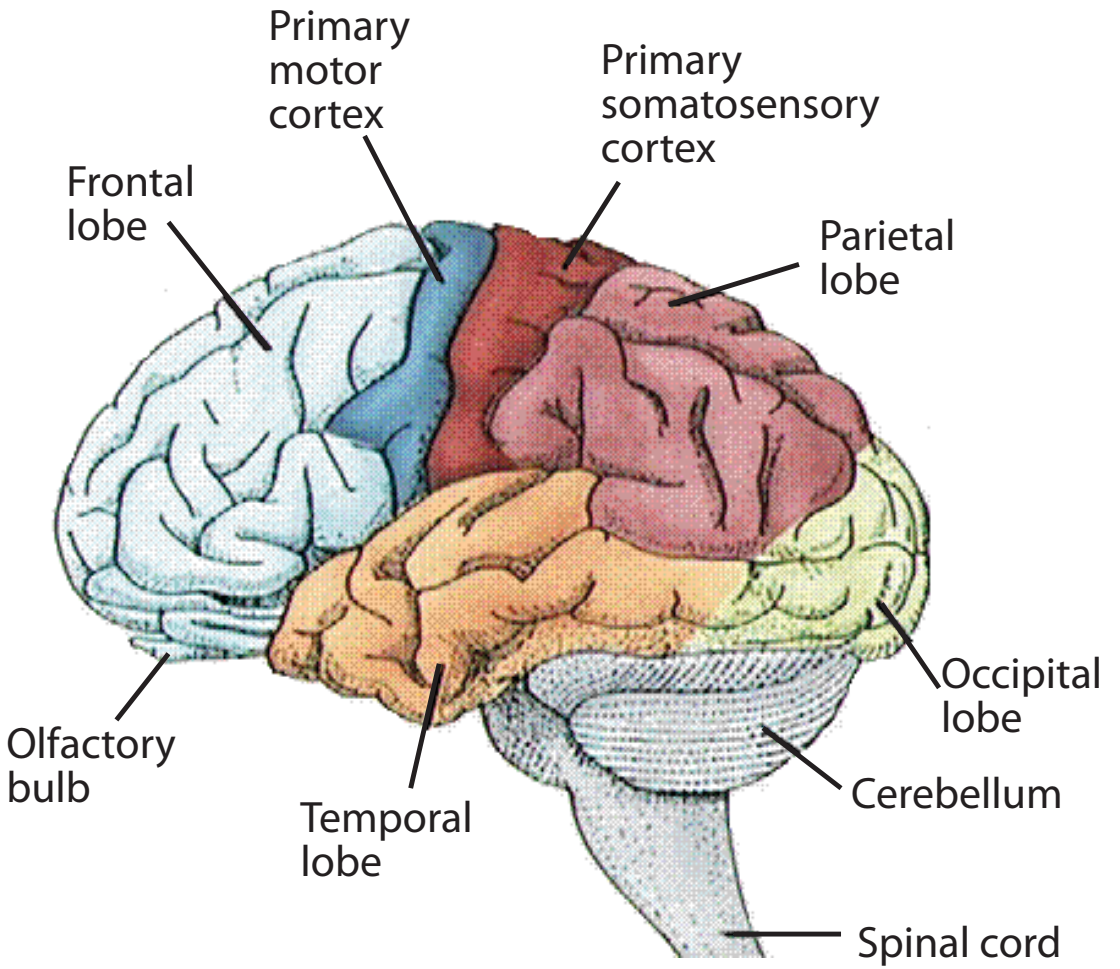




What are the brain circuits controlling the selection of actions?

The cerebral cortex forms a network with the basal ganglia that helps us choose what to do and think...



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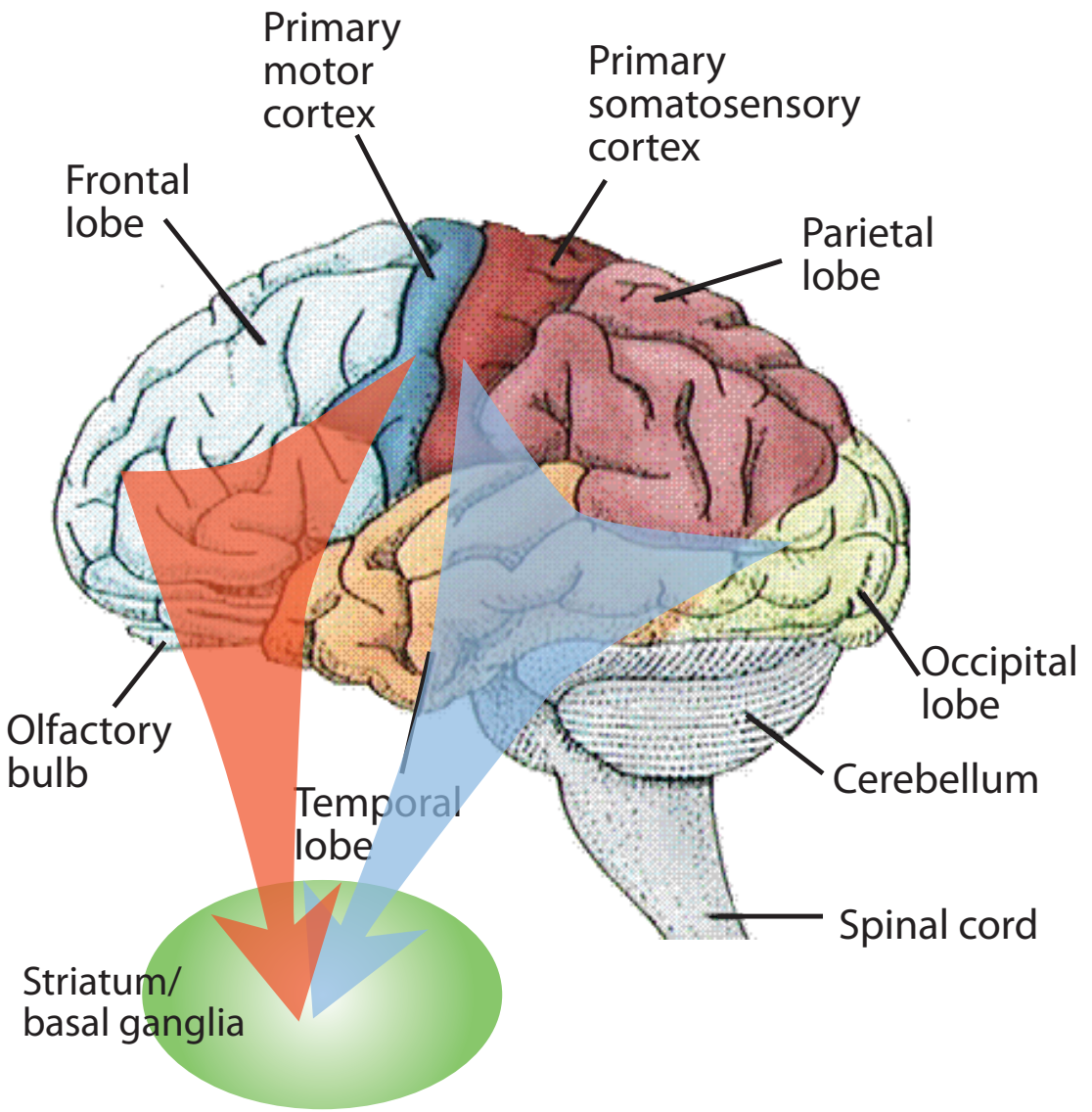

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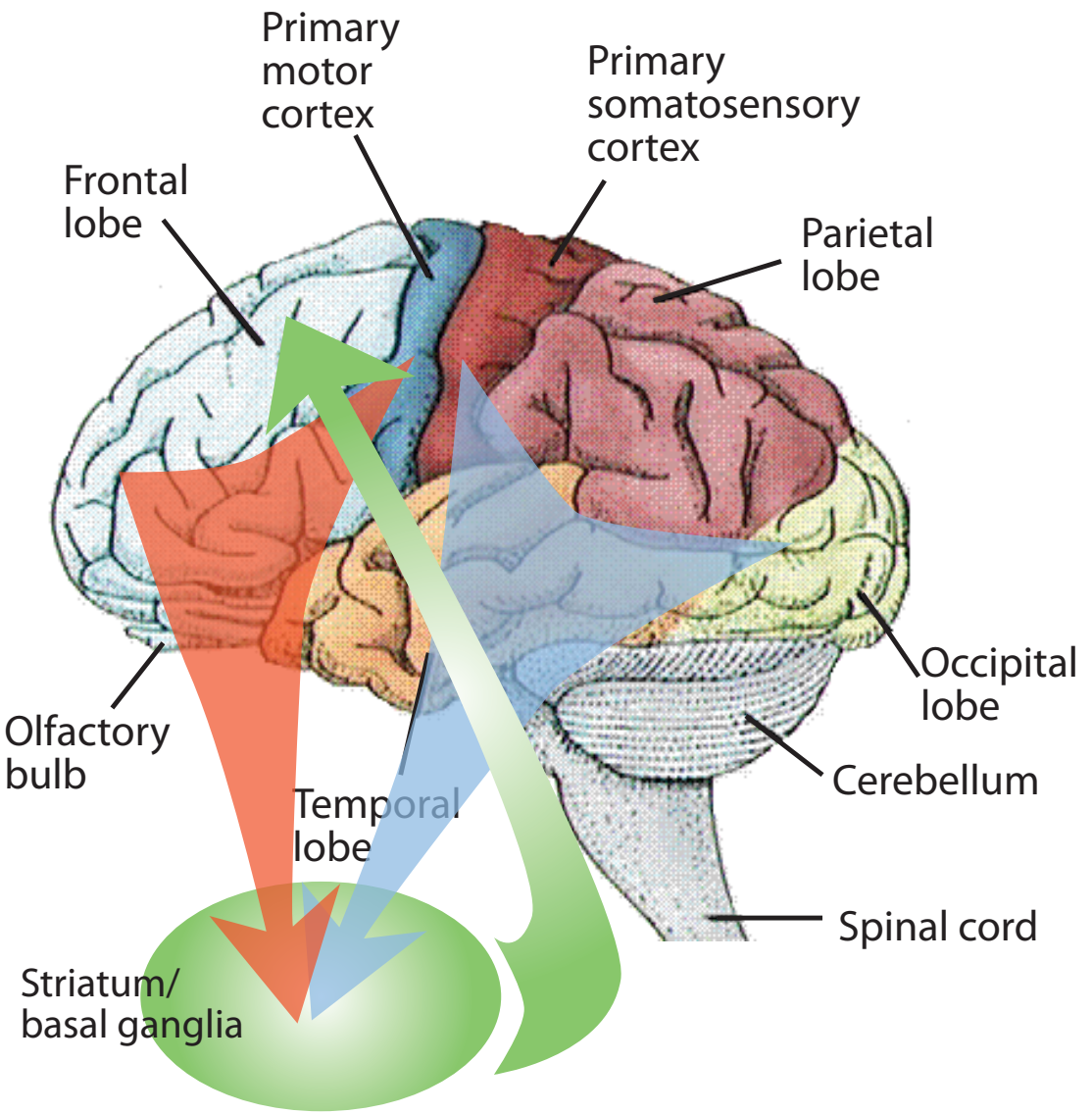

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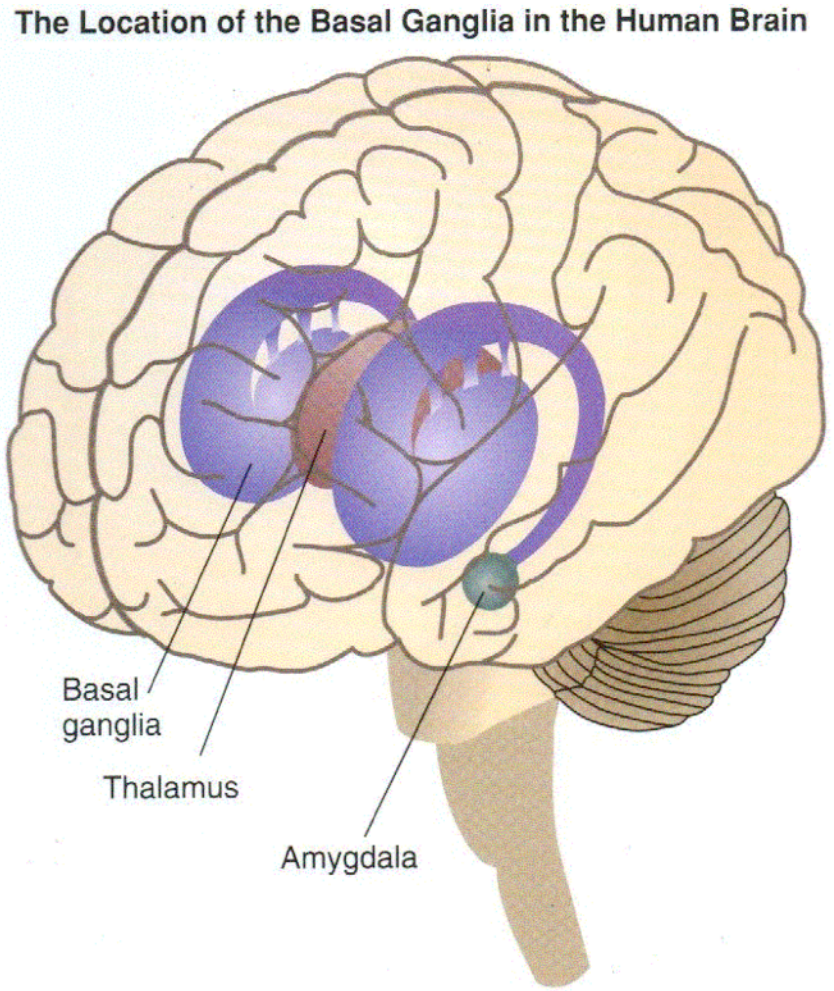

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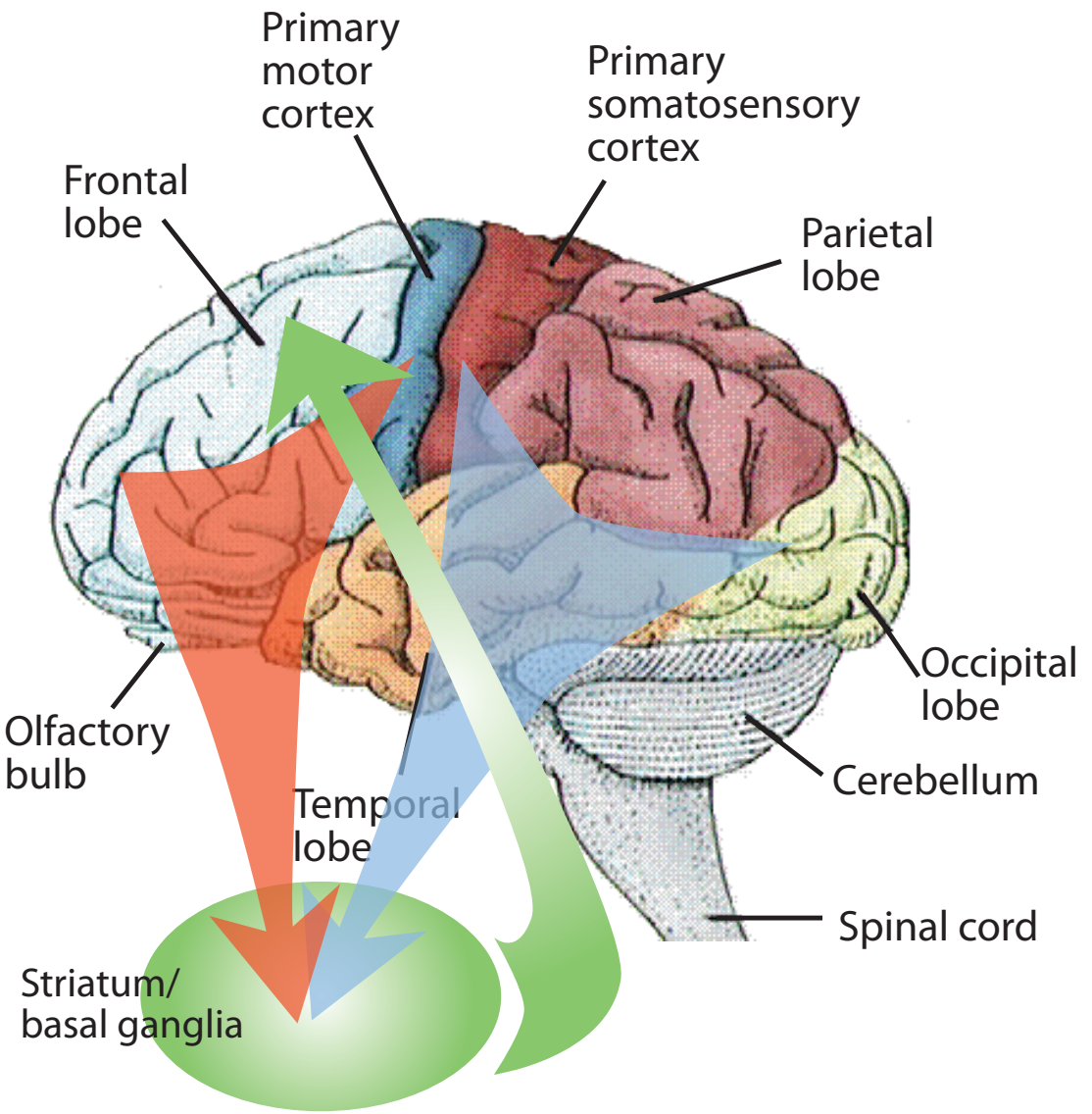

Think about the cerebral cortex as the ‘commander-in-chief’ and the basal ganglia as a trusted advisor...

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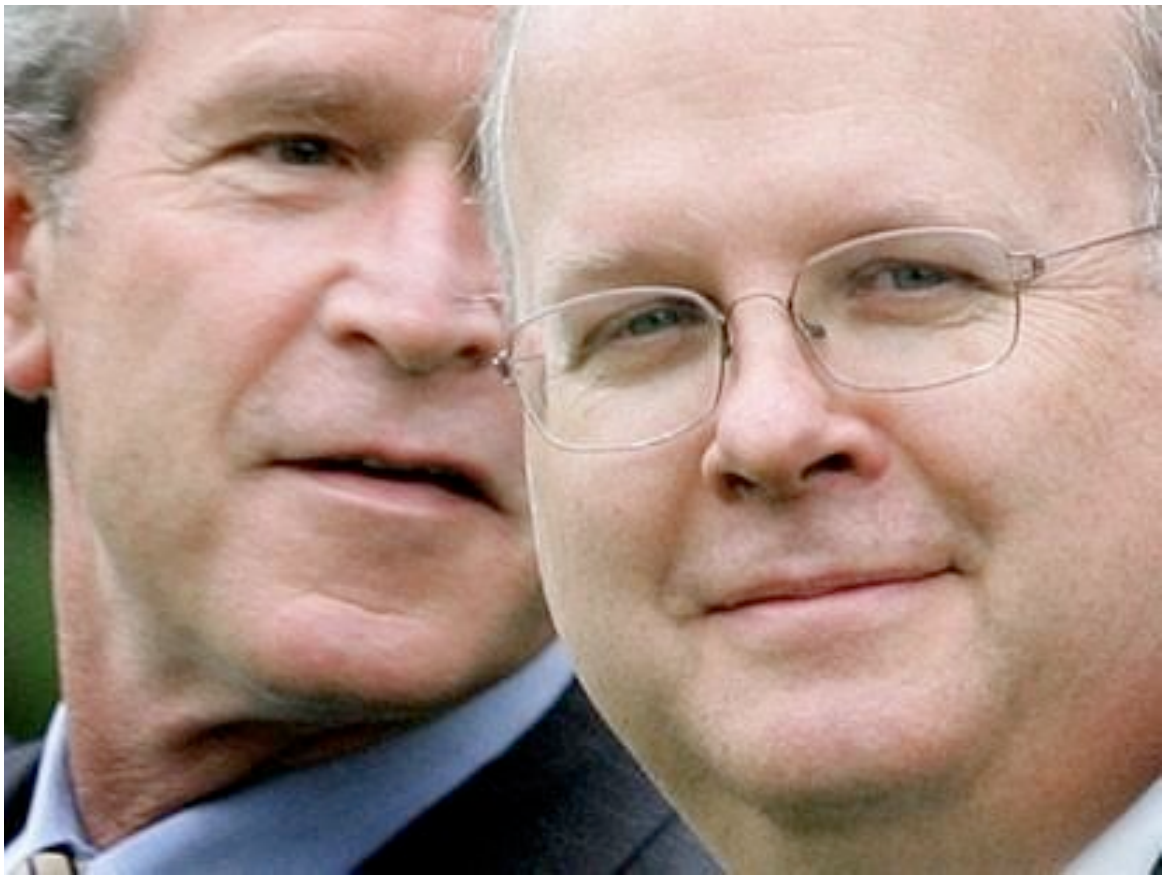
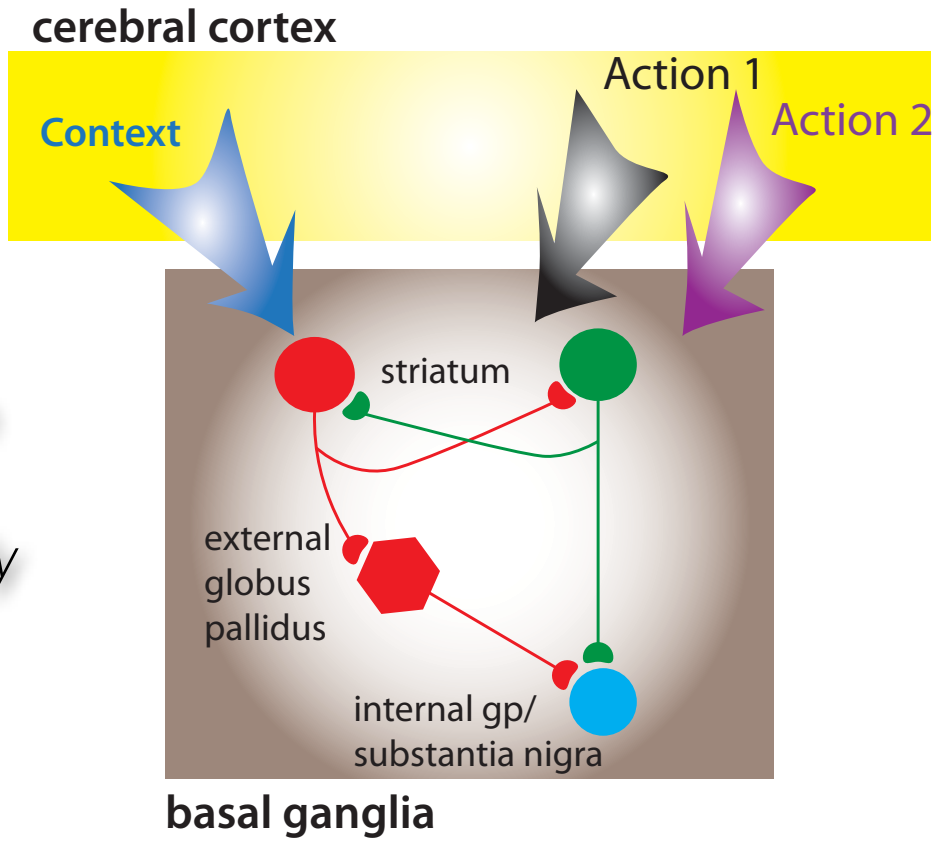


Dopamine release in the striatum helps the basal ganglia choose how to act in a way that maximizes our pleasure and minimizes our pain...

Basal ganglia control circuits

What should I do?

What worked in the past? What is currently working?



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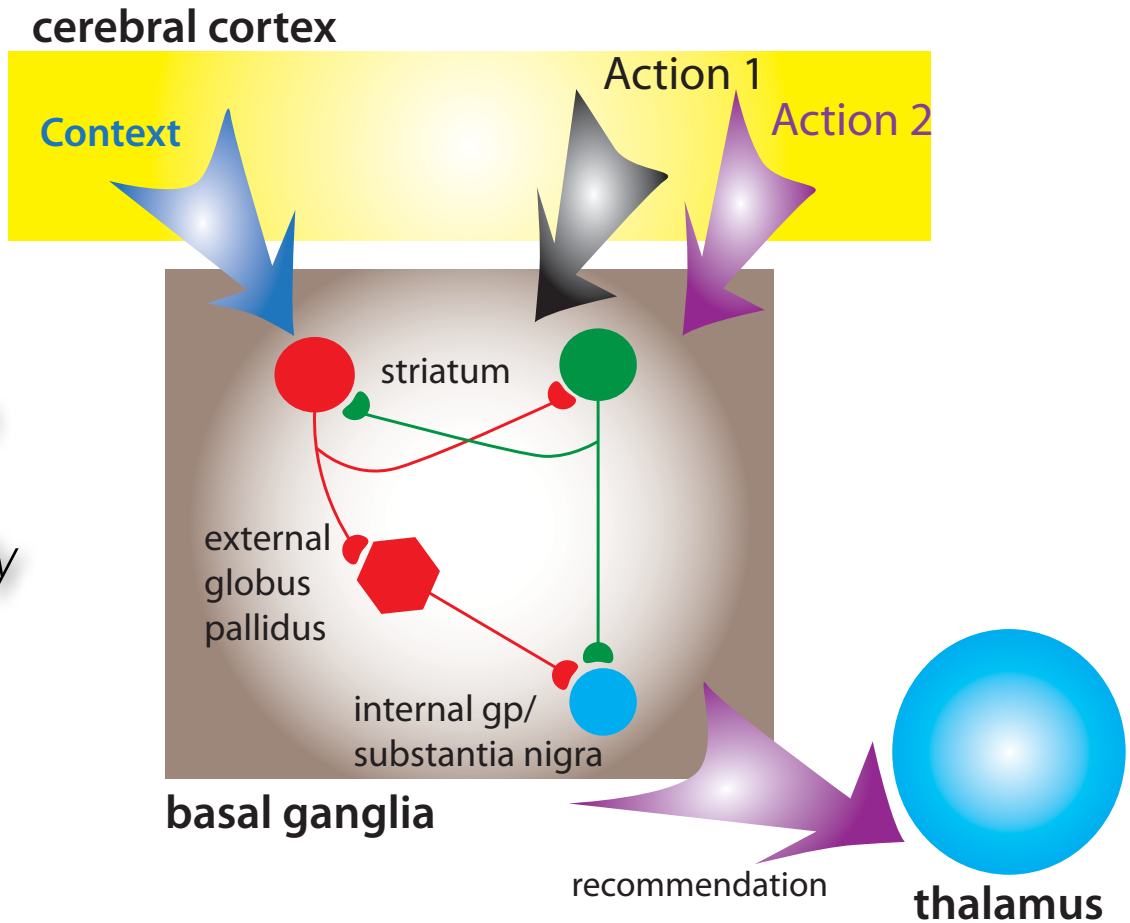

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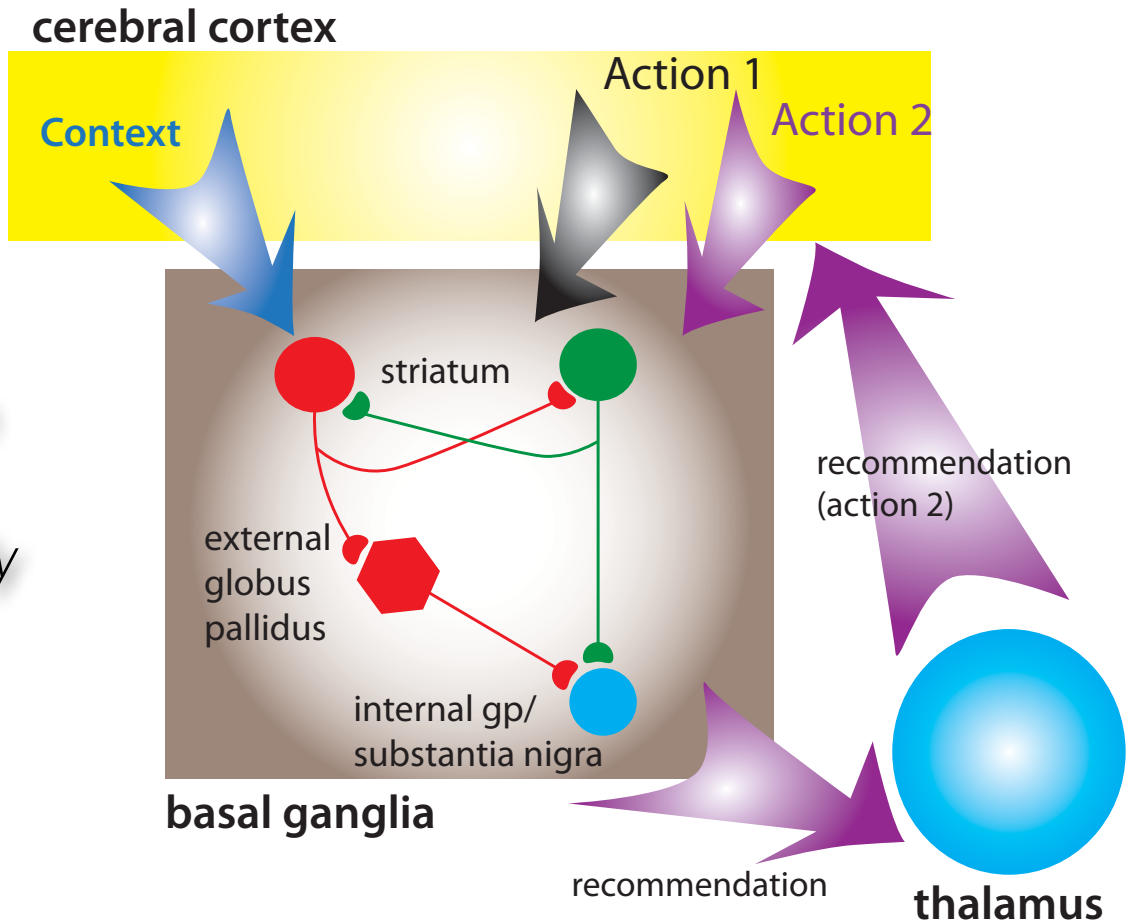

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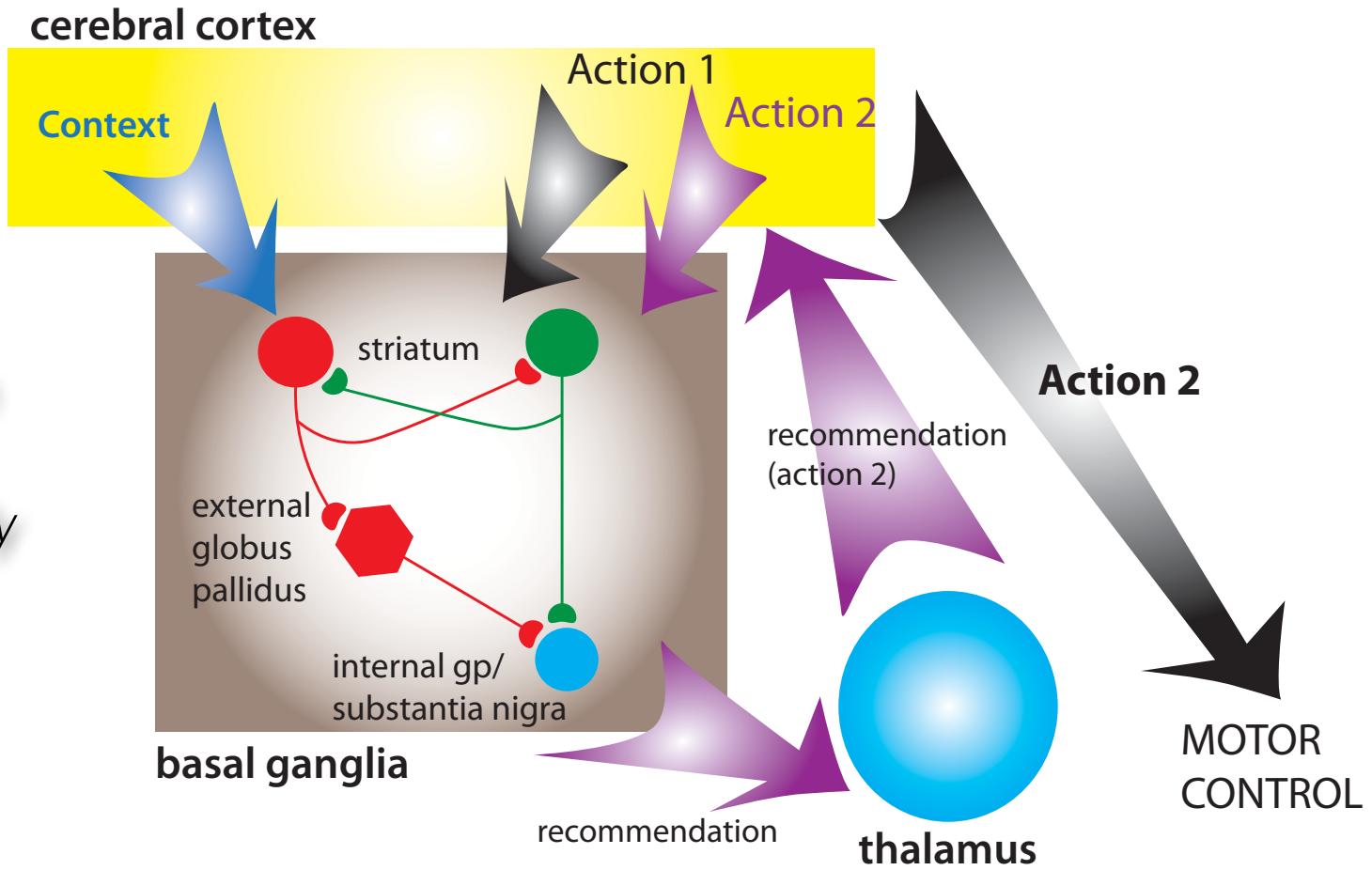

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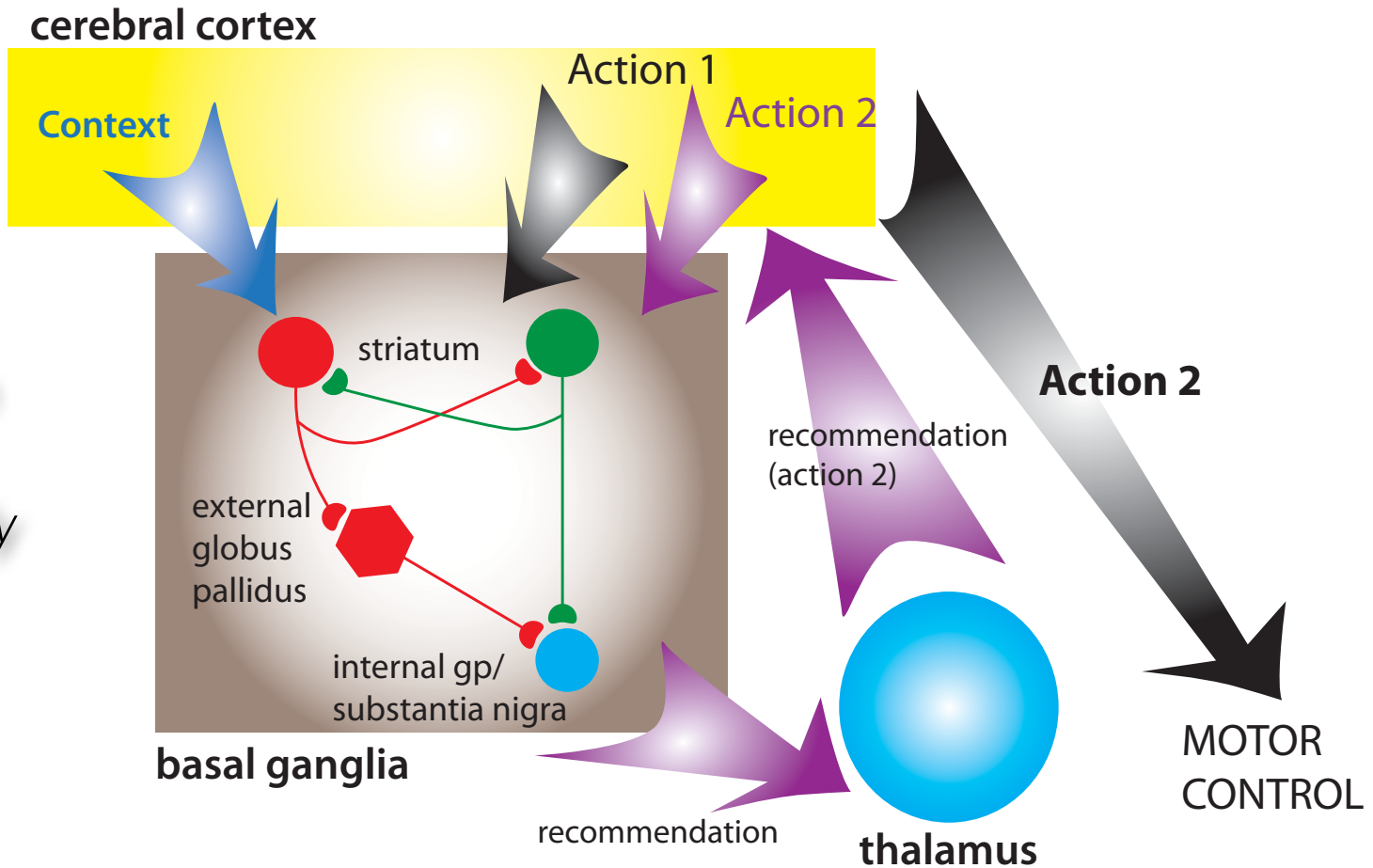

Feedback is provided by dopaminergic neurons that monitor reward/punishment...

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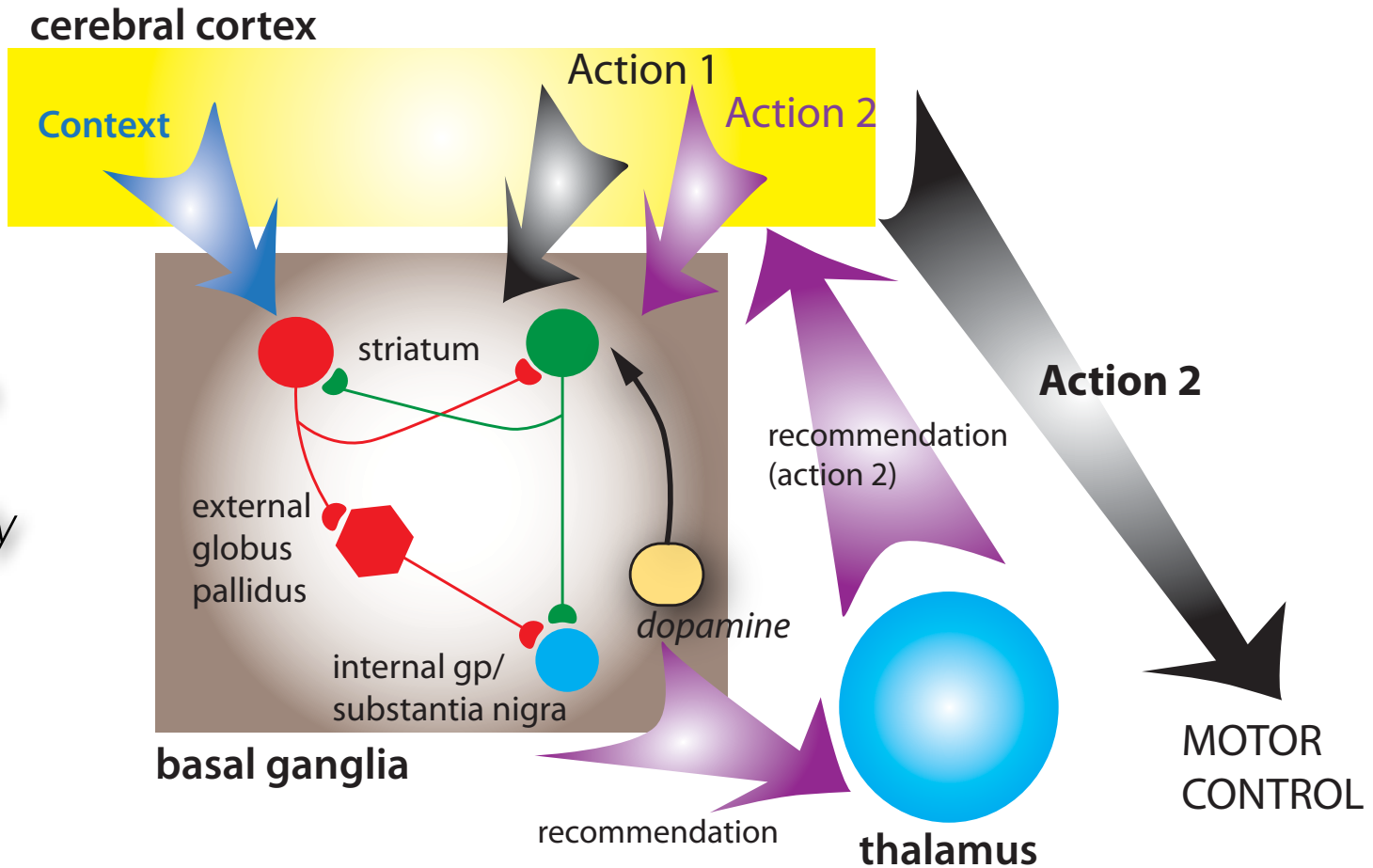

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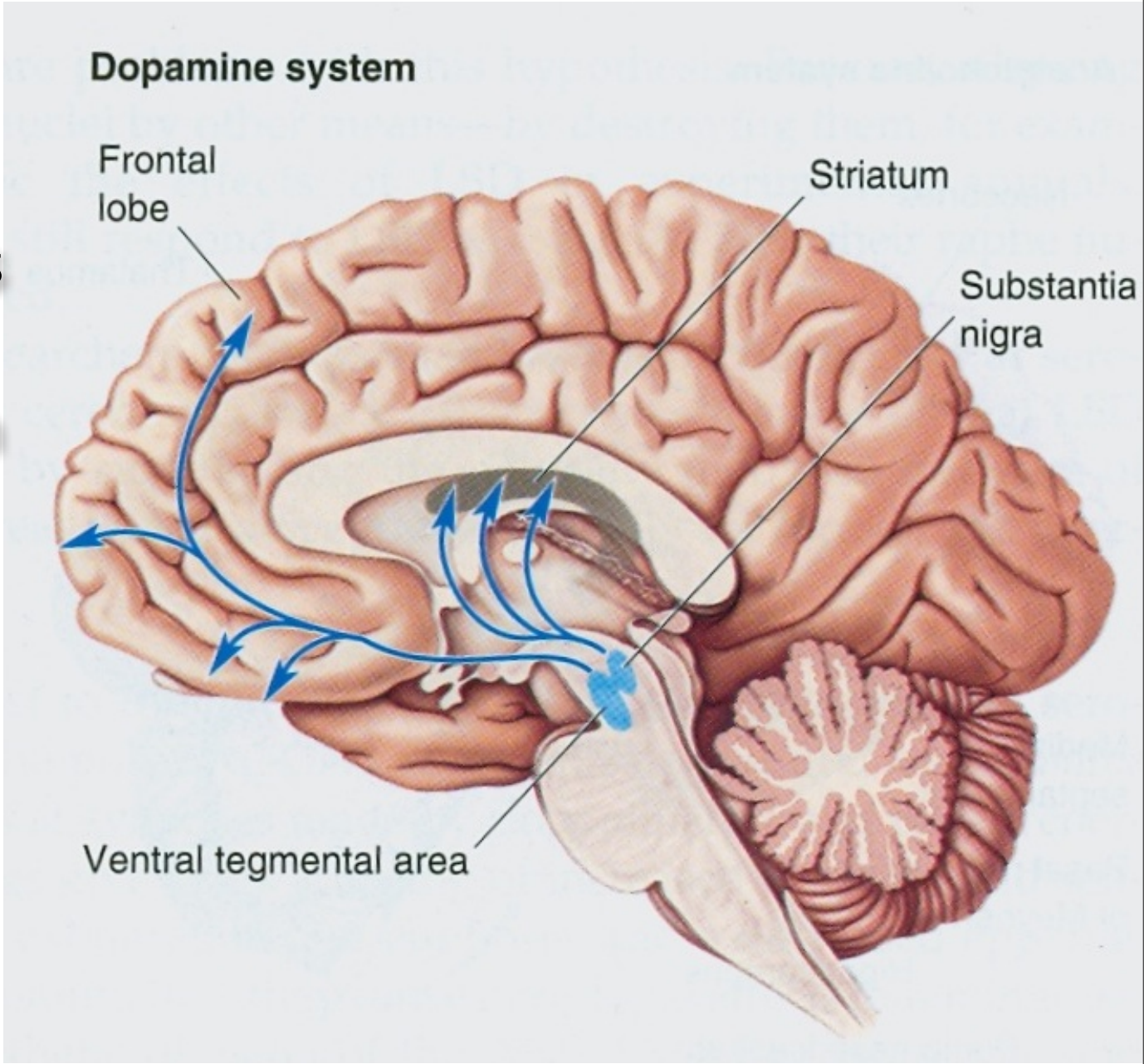
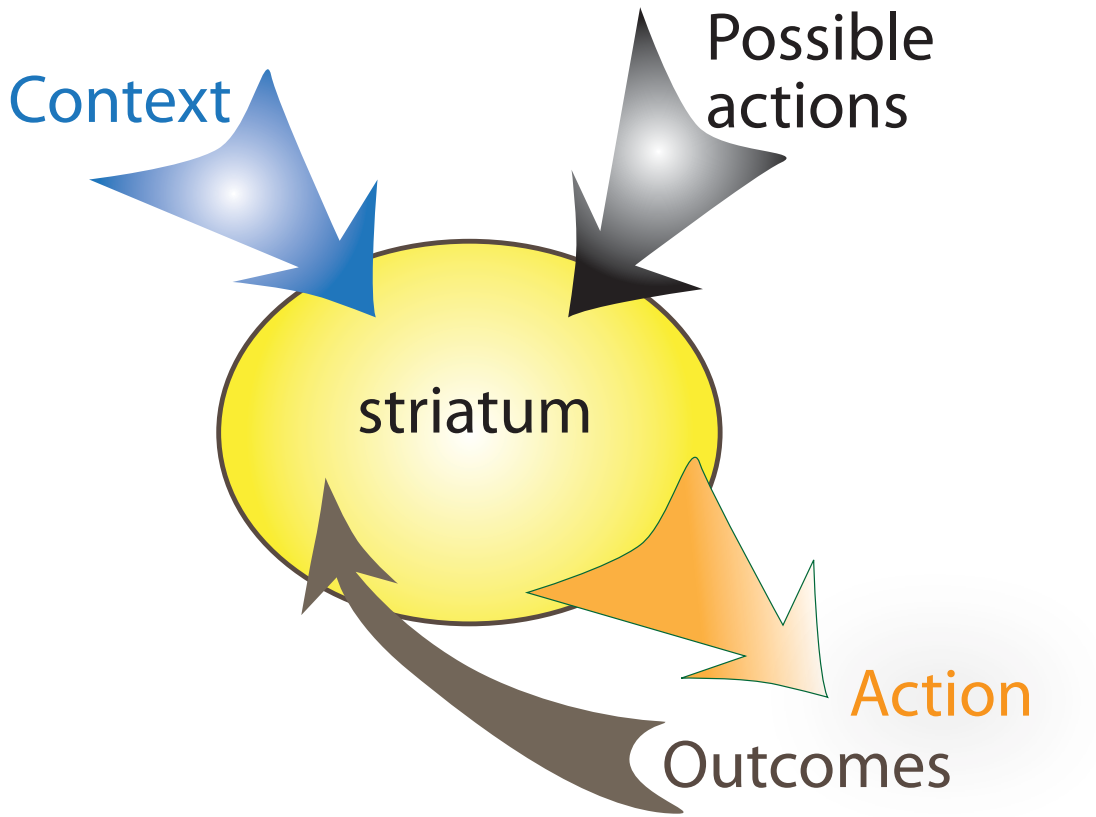
Striatal neurons engaged in action selection talk with neurons that release dopamine...

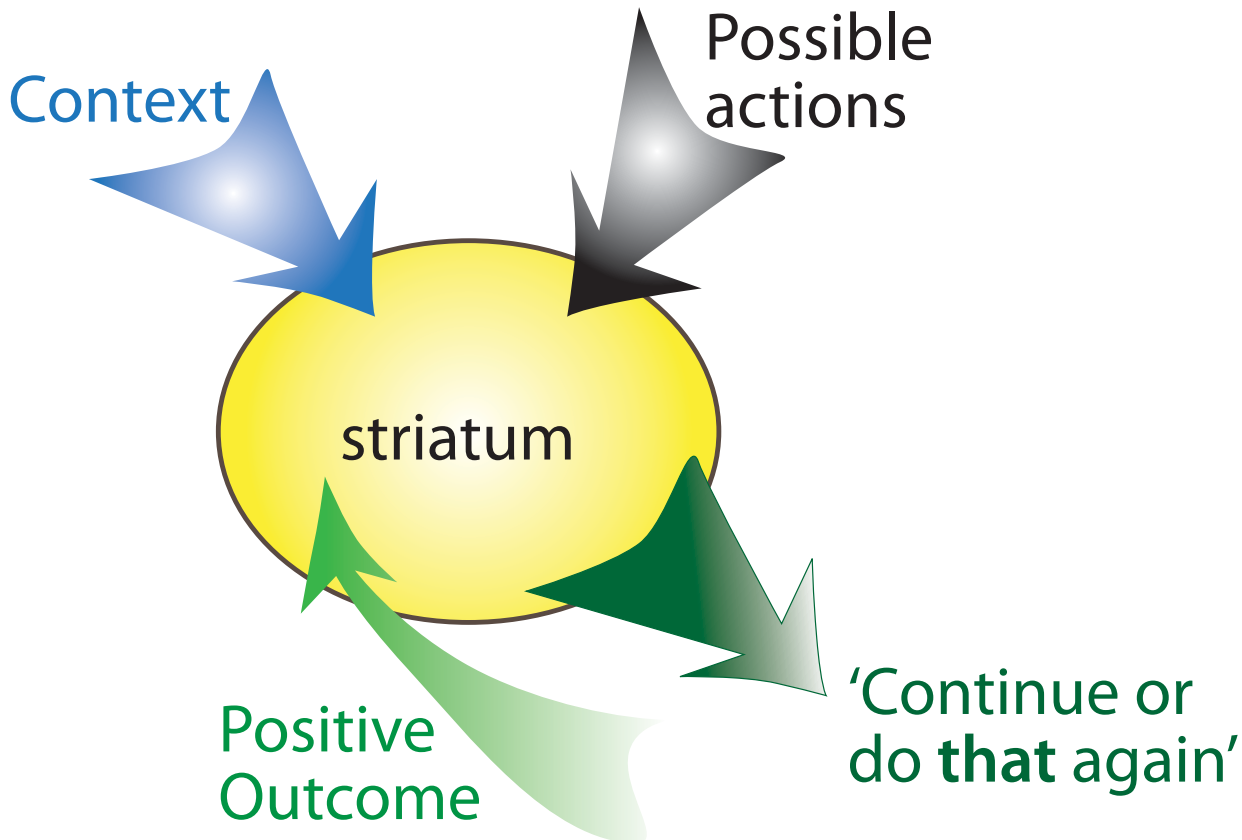


adapted from Bear et al., 2001

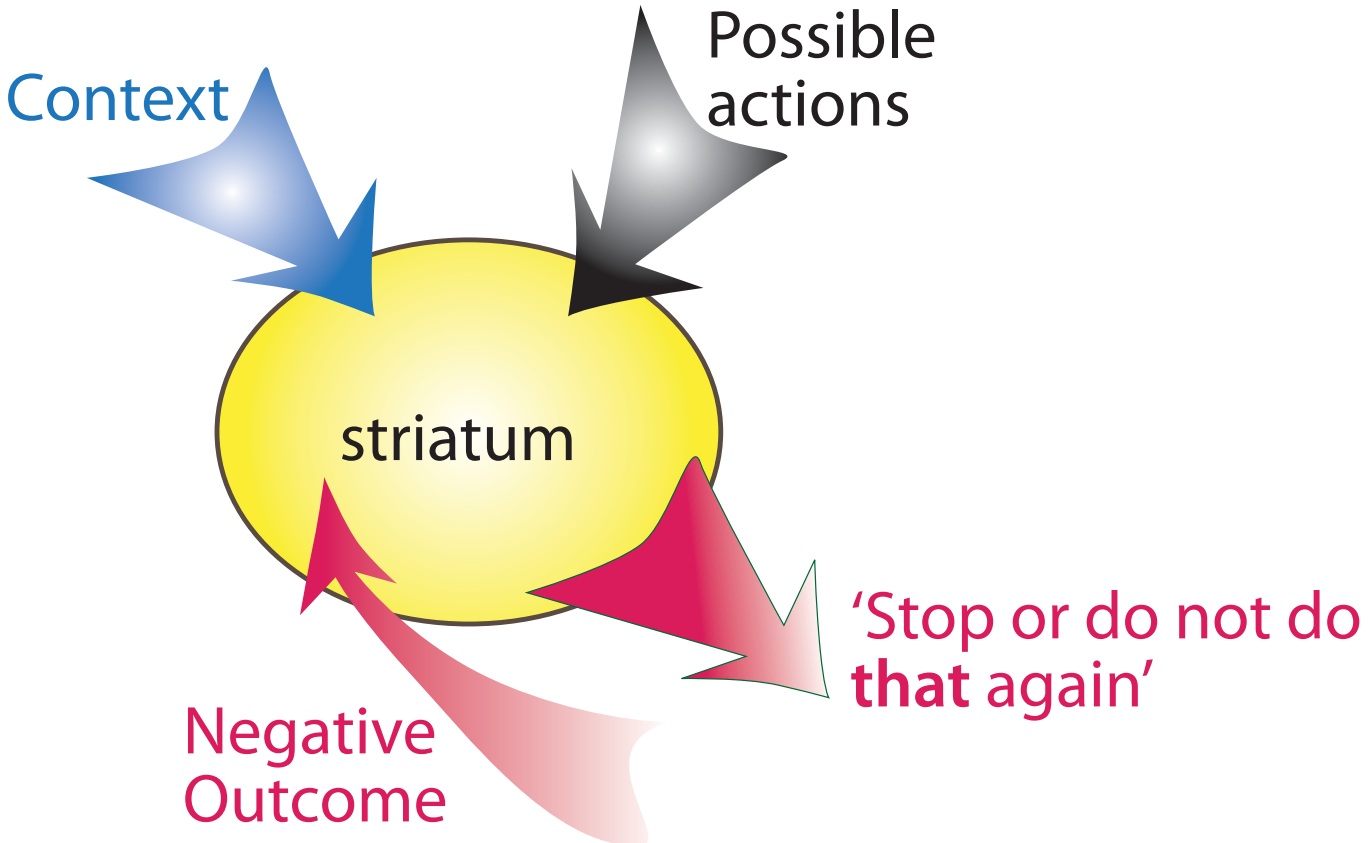
Dopamine helps the striatum choose the right action in the right context...



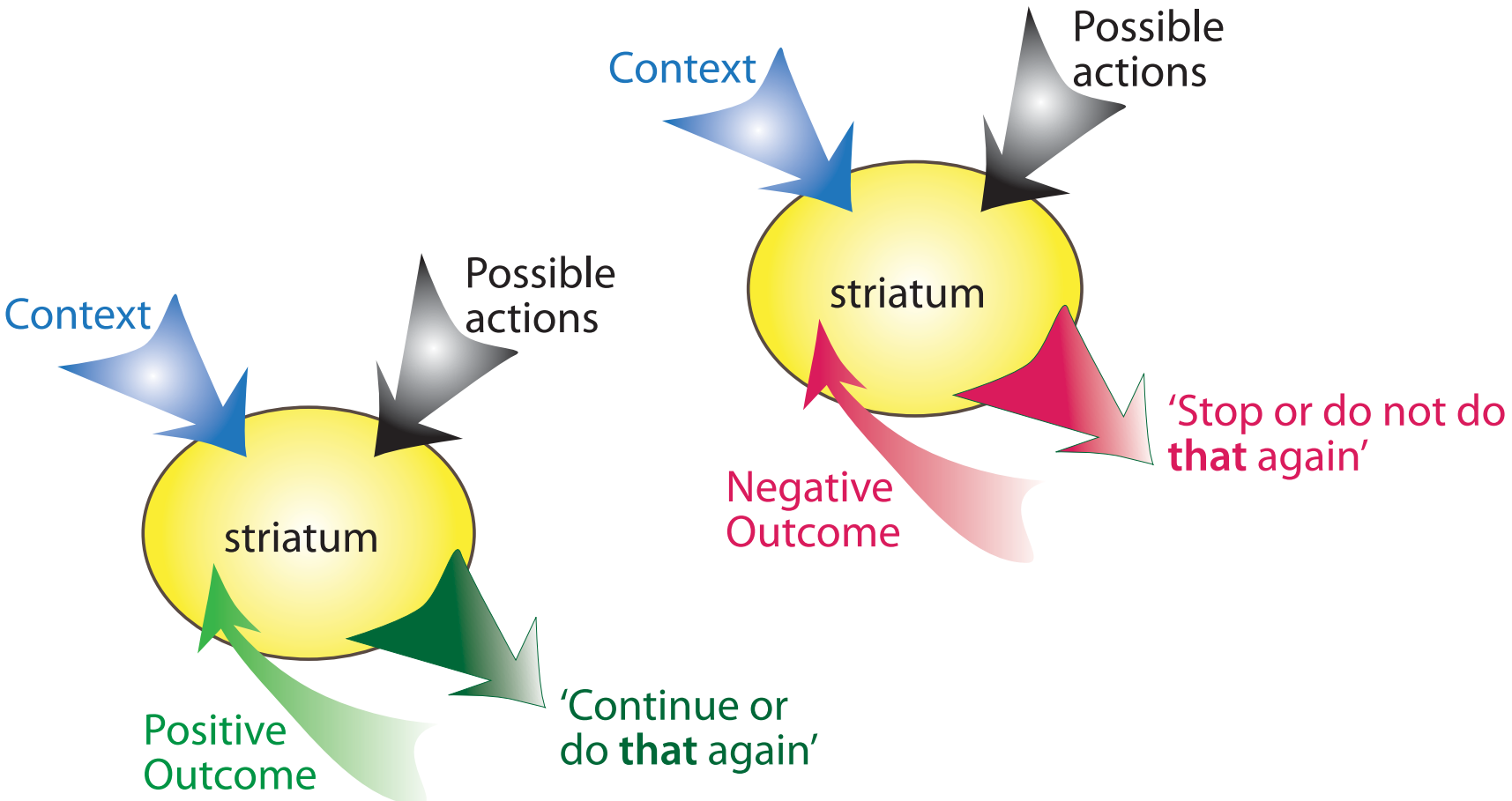
Sometimes this means choosing a particular action...



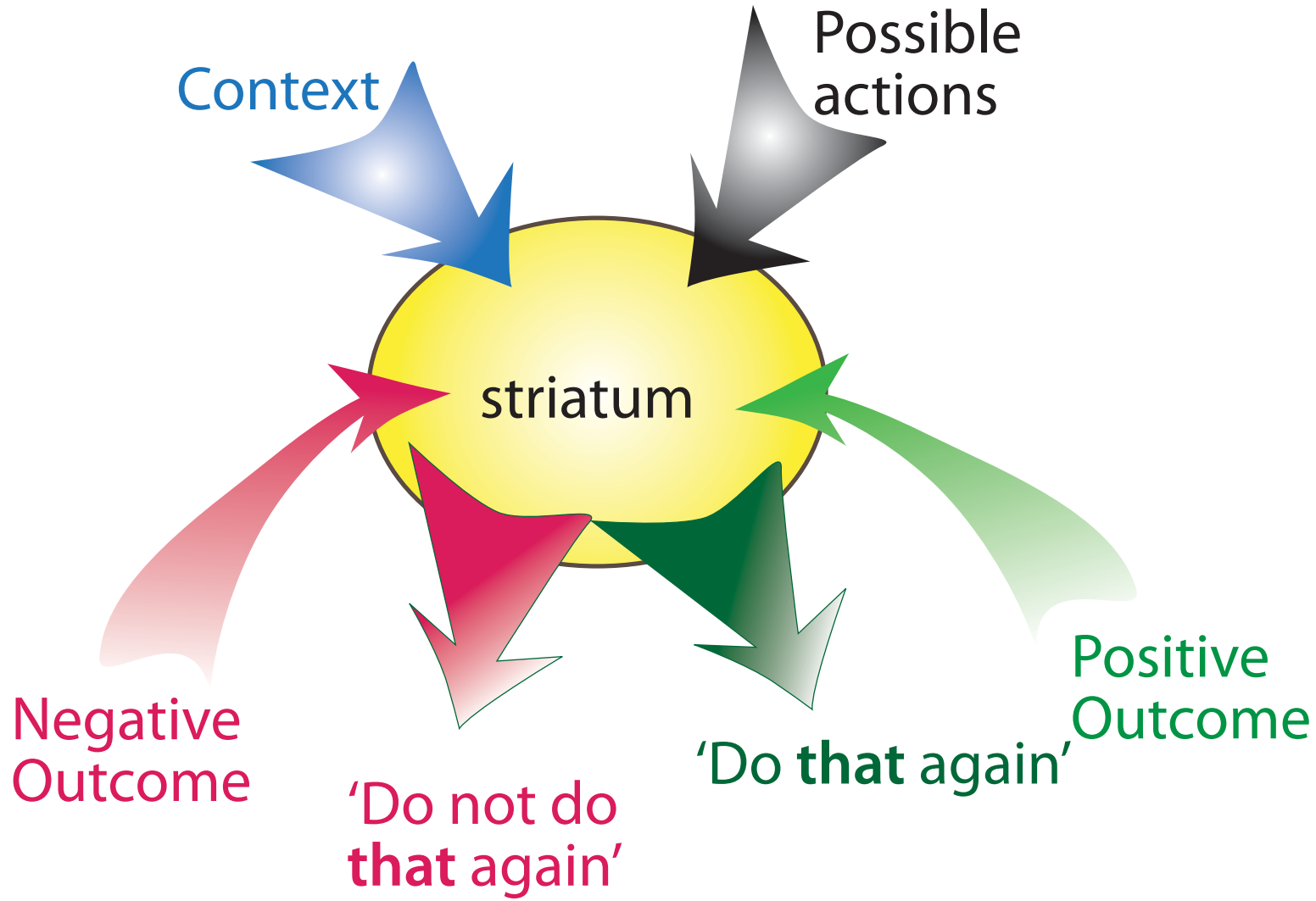
Sometimes, this means **not** acting in particular way... .



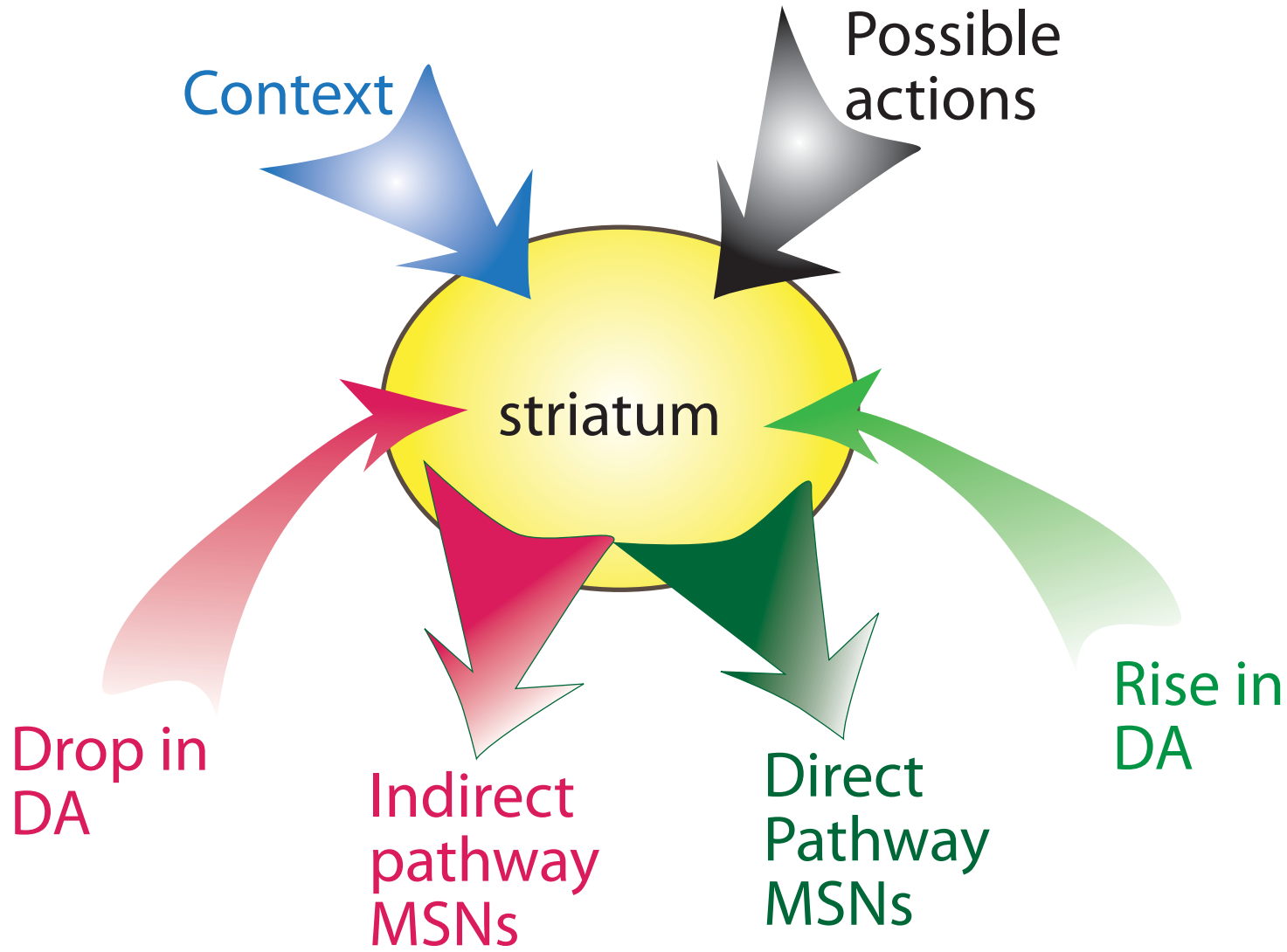
How can the circuit be designed to accomplish both goals?



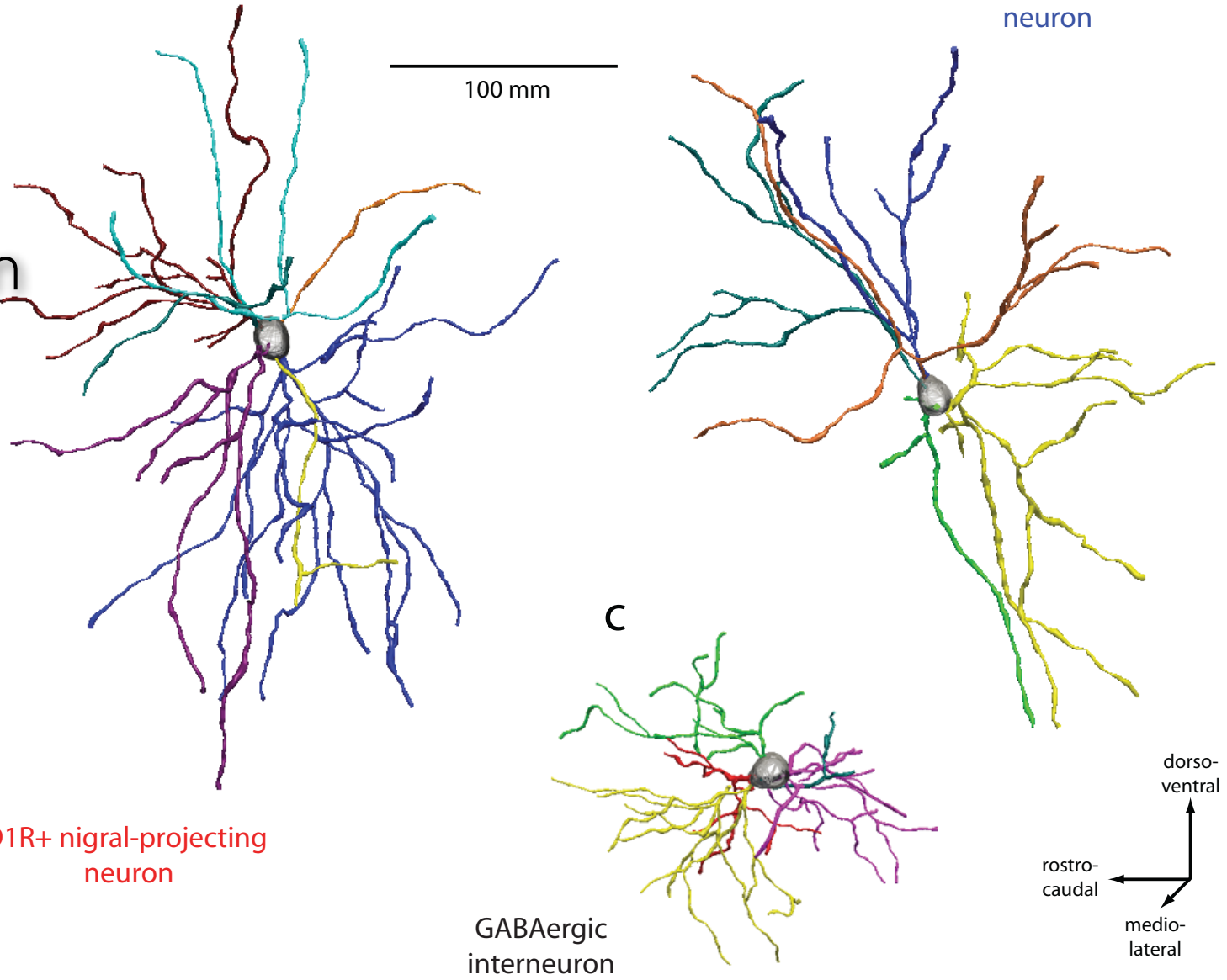
One way to construct a network with this functionality is to have two subsystems....



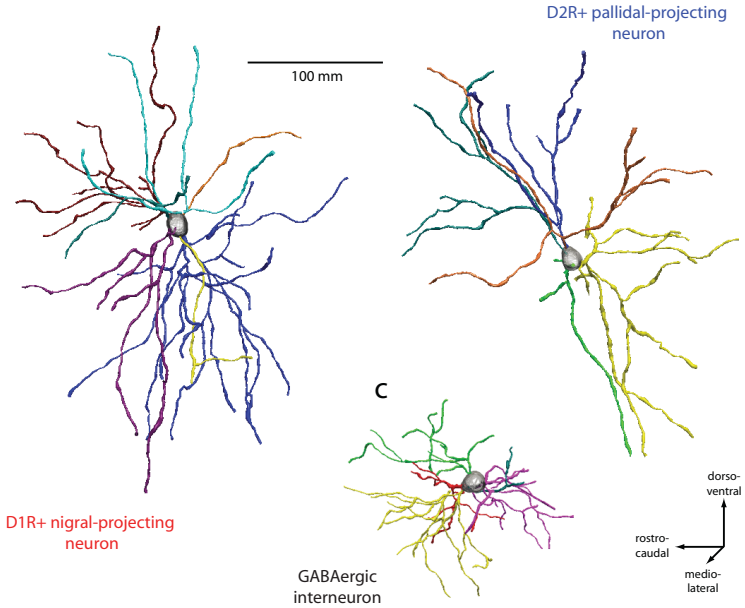
In fact, this is the way the striatum is constructed....

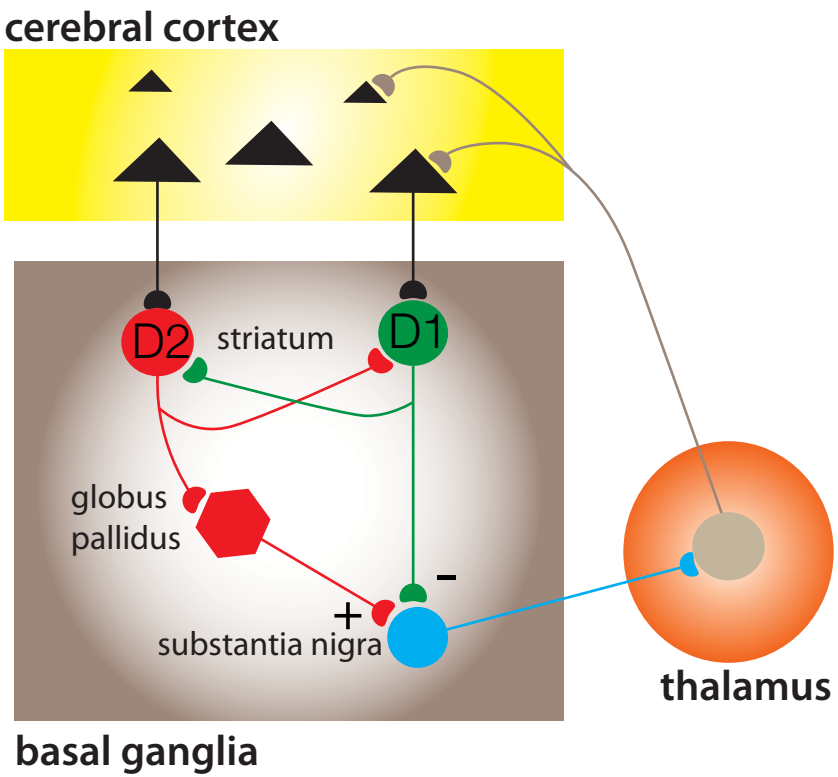


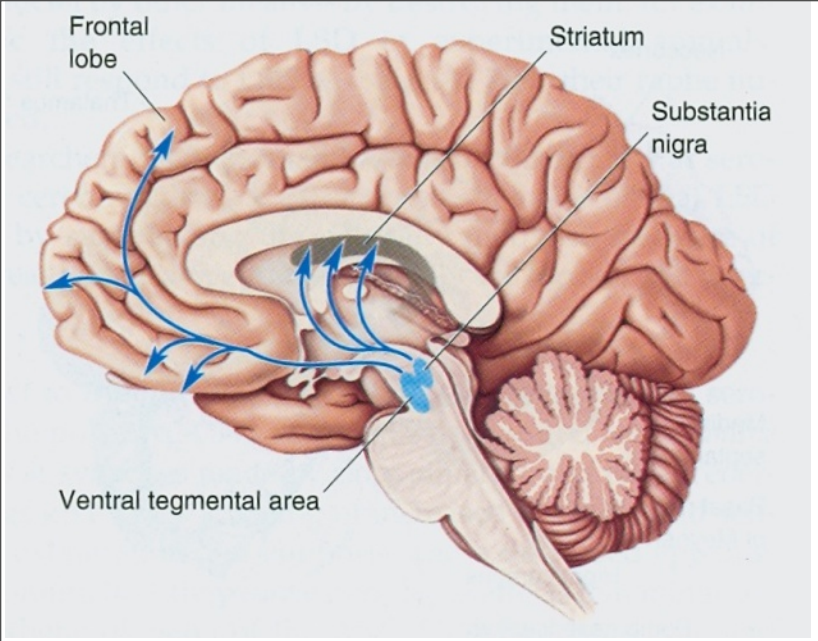
Striatal neurons that differ in their expression of dopamine receptors anchor these circuits...

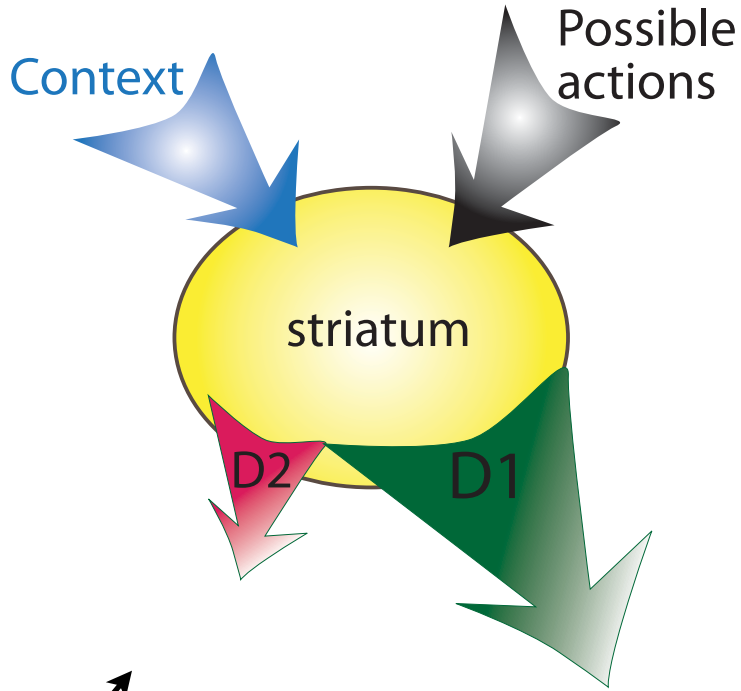


These two cell types are wired to produce a complementary influence on the thalamus...

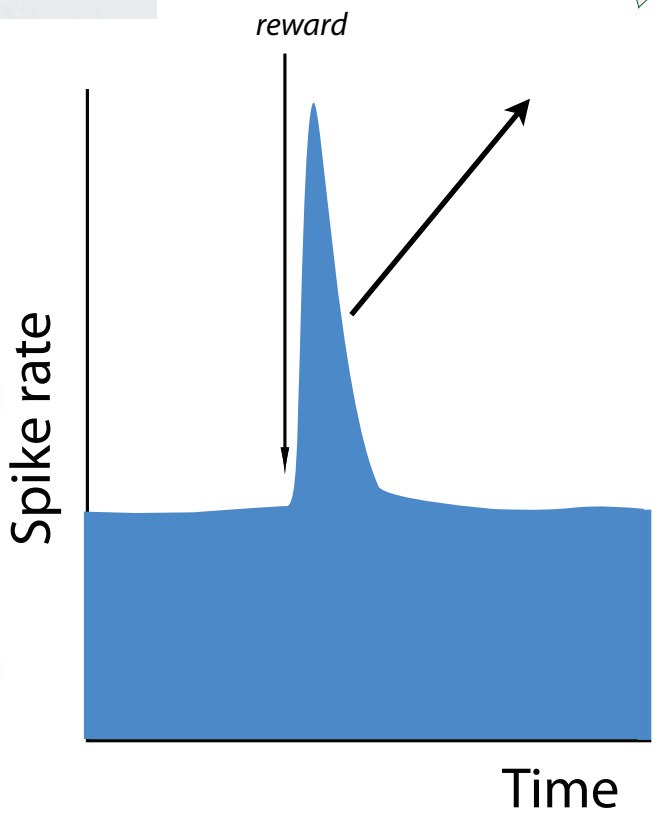


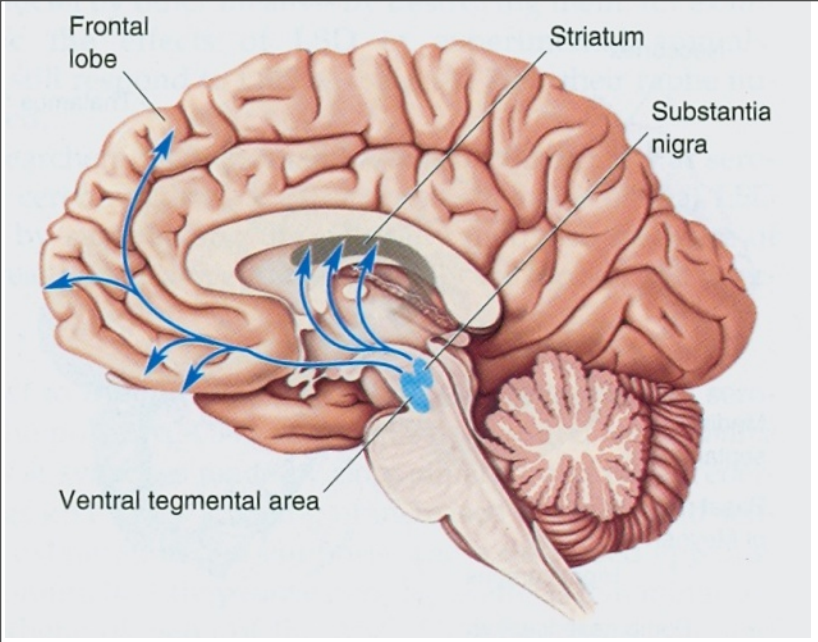


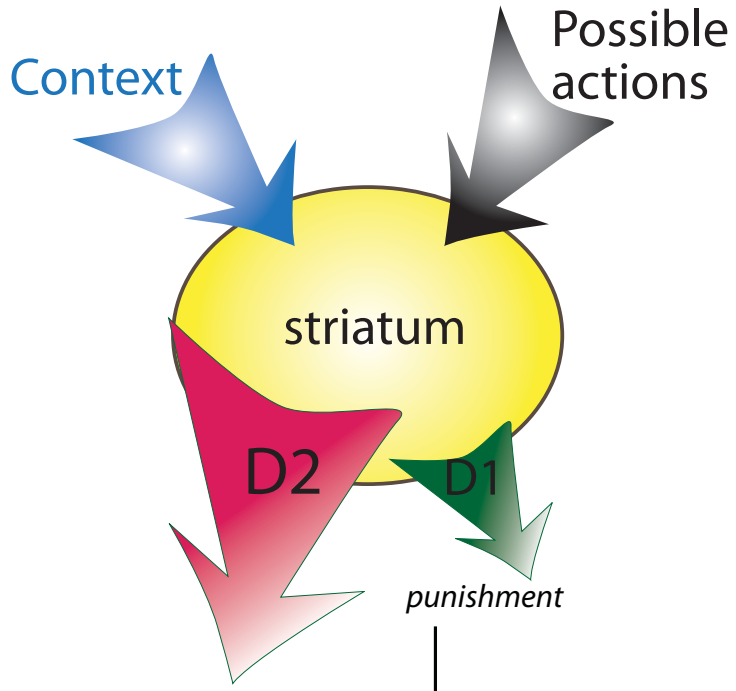




Because principal neurons express different receptors, they respond to dopamine release in opposite ways...







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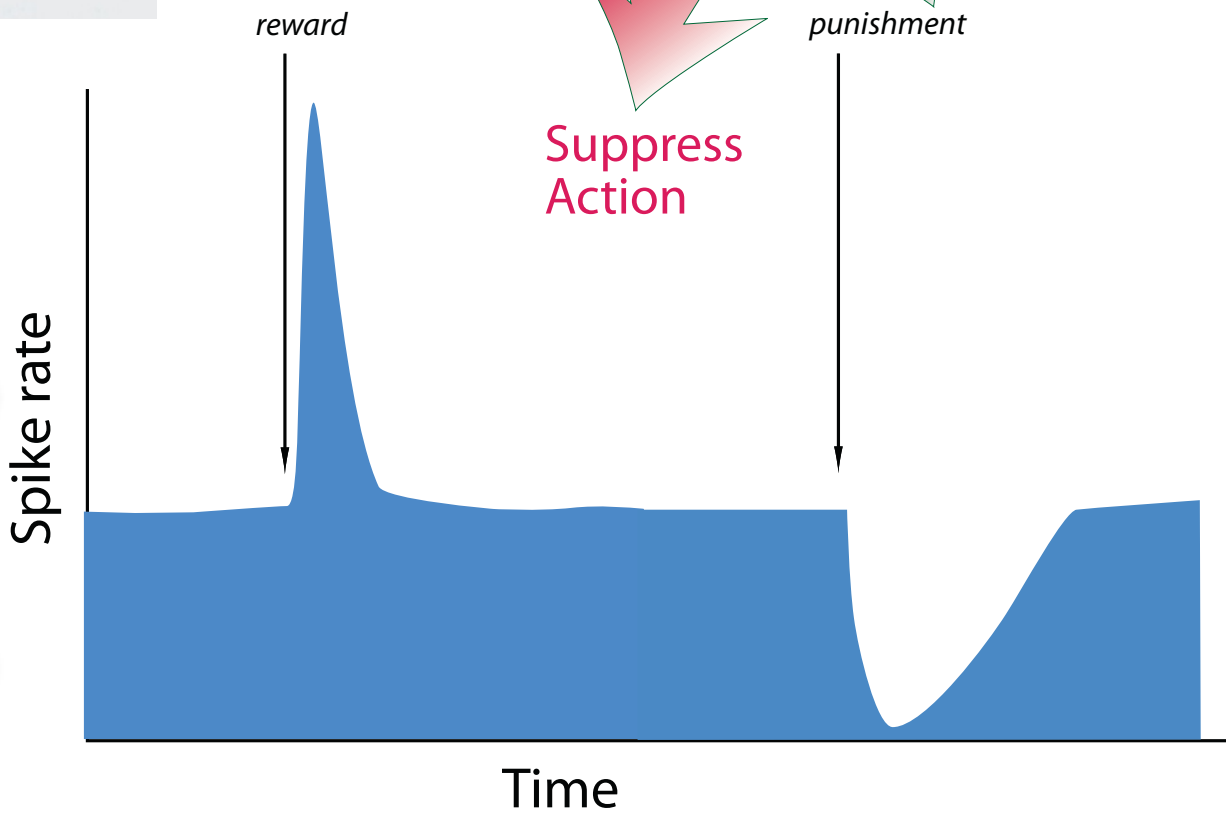
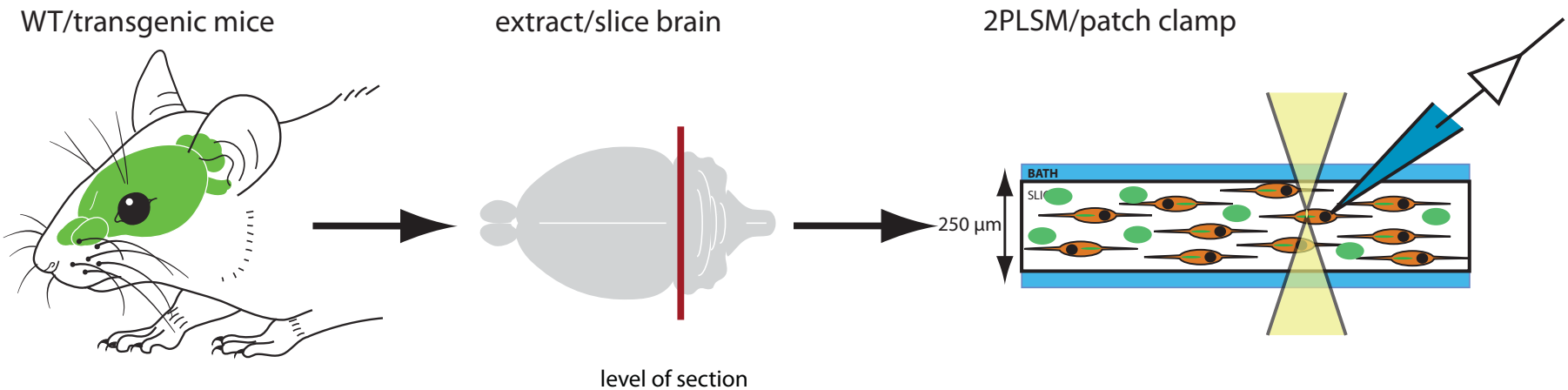
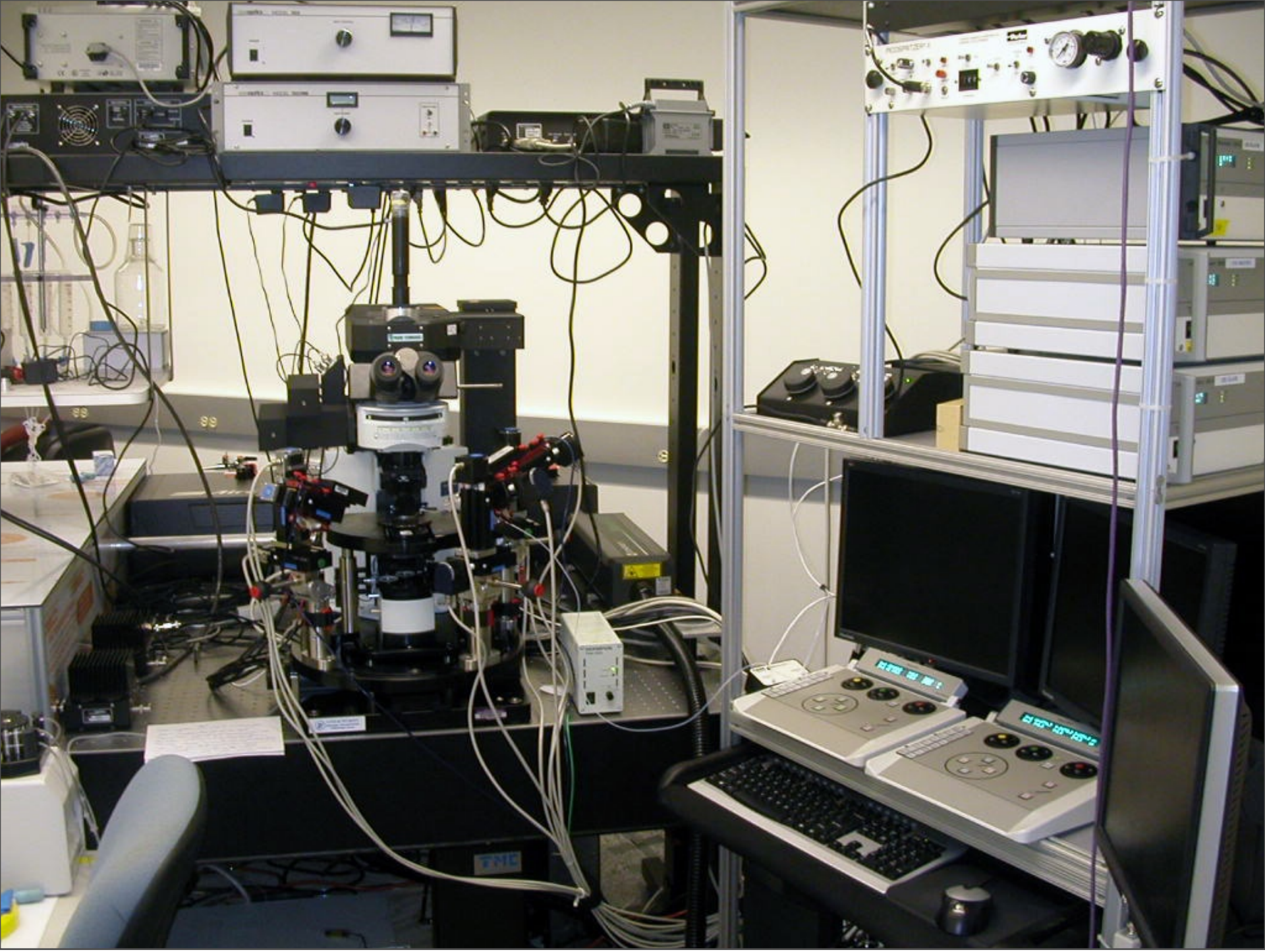


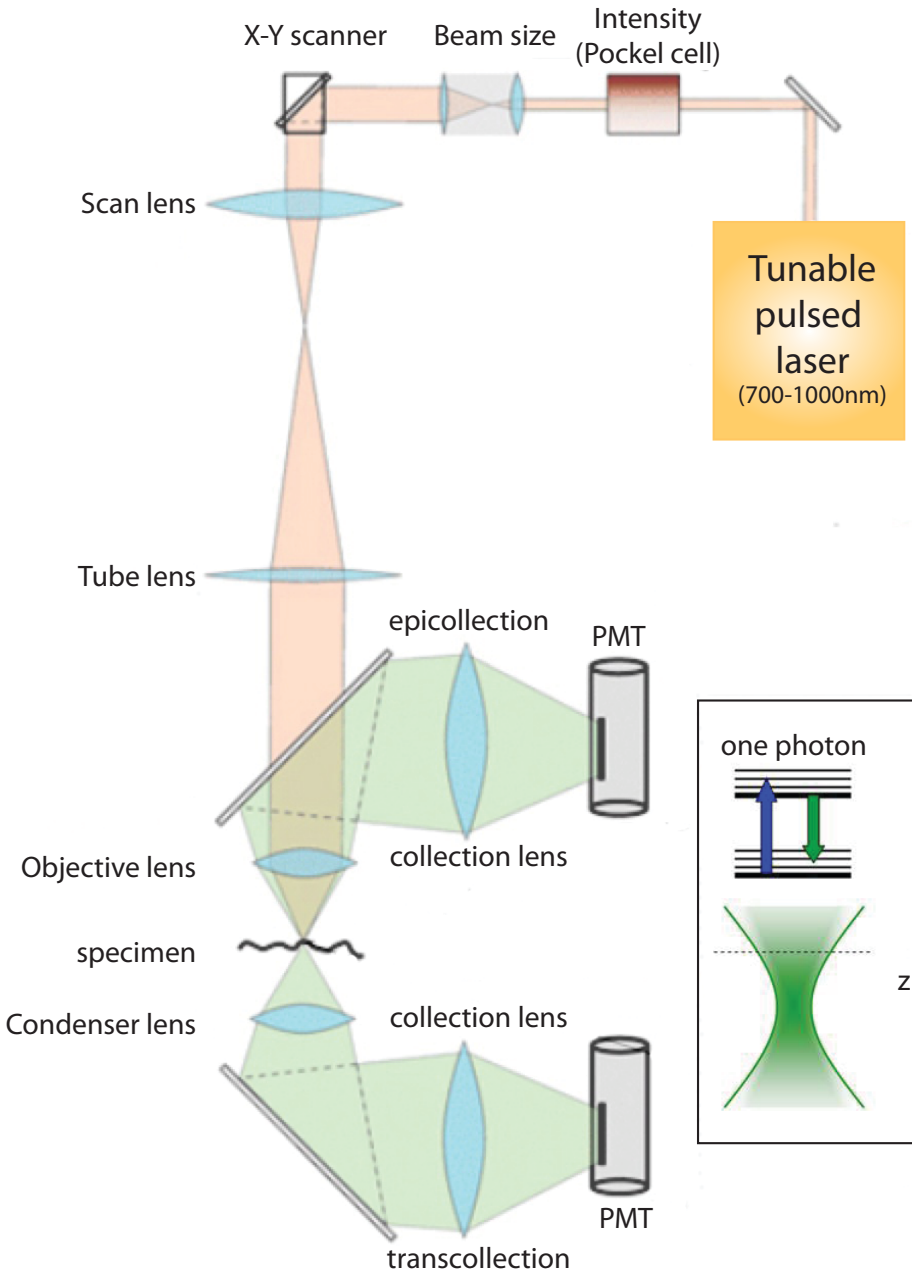
How dopamine controls striatal function is a major focus of our lab...

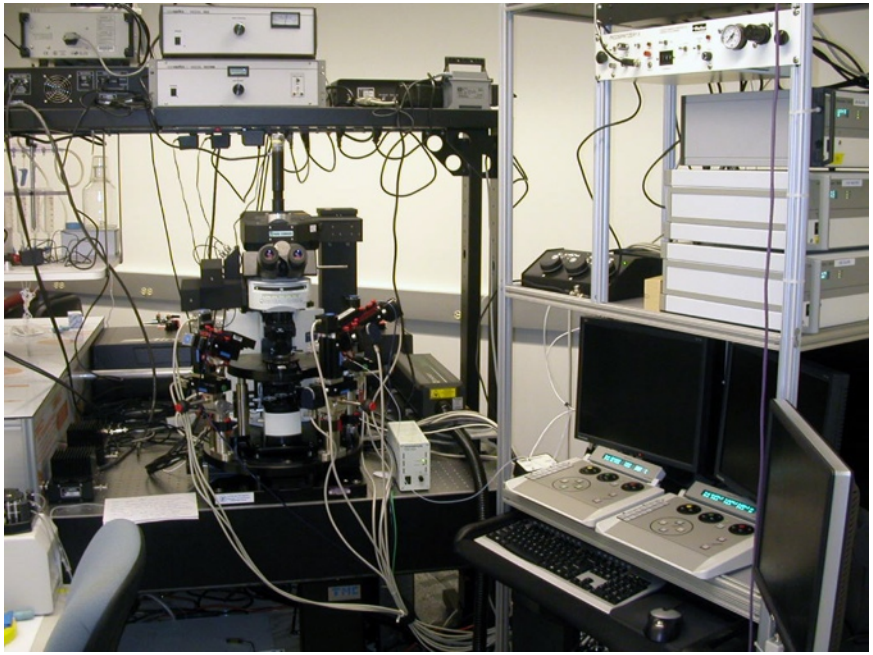
We use optical and electrophysiological techniques in brain slices from transgenic mice to characterize neuronal function...

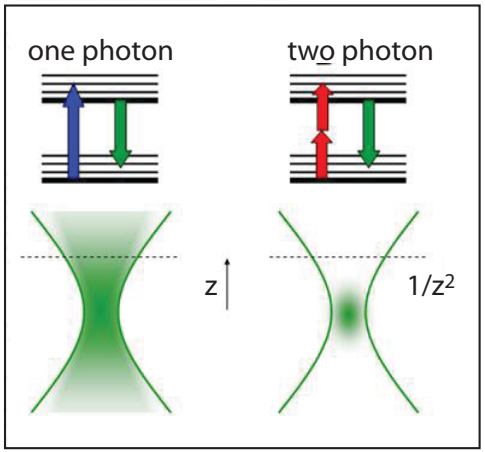




Tuesday, January 18, 2011







2P imaging has the advantage of being able to ‘see’ deep without producing damage.

These techniques can be used to image living neurons and to monitor their behavior...

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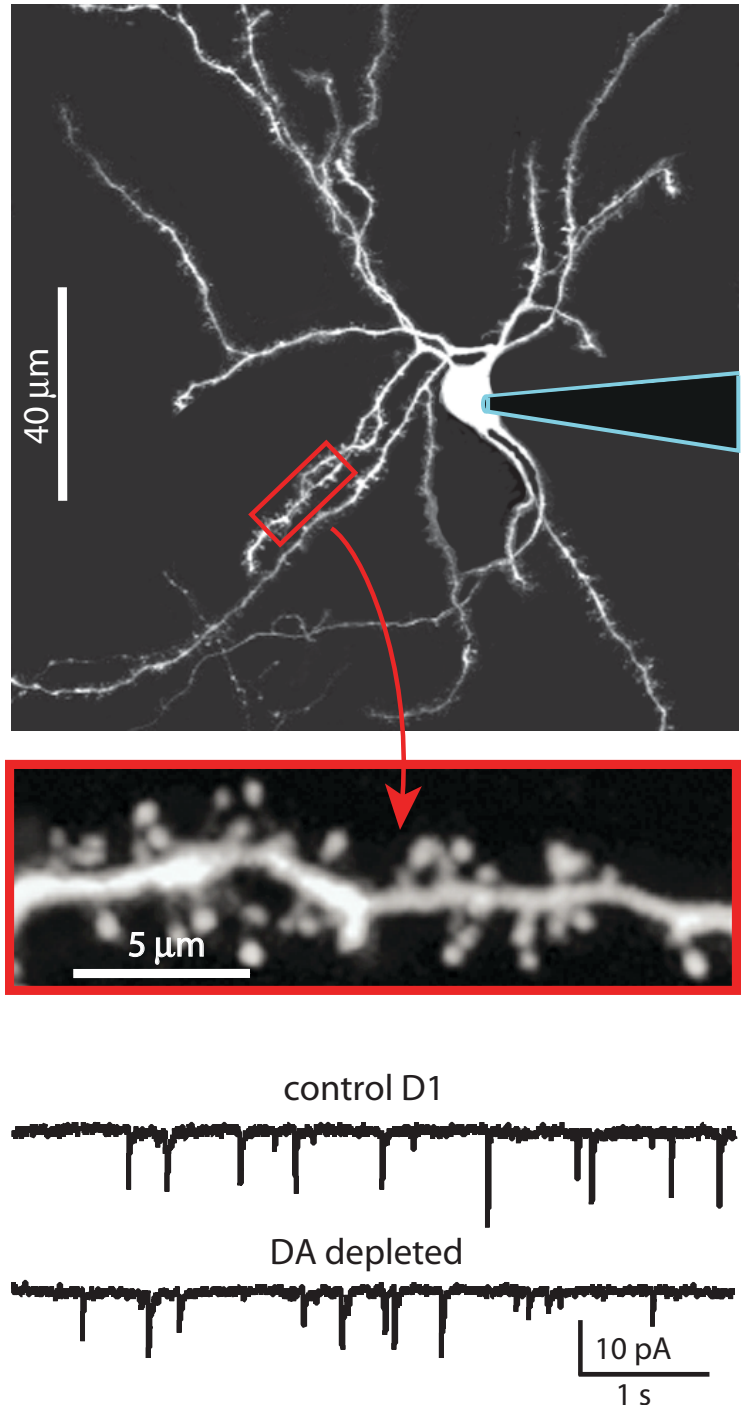

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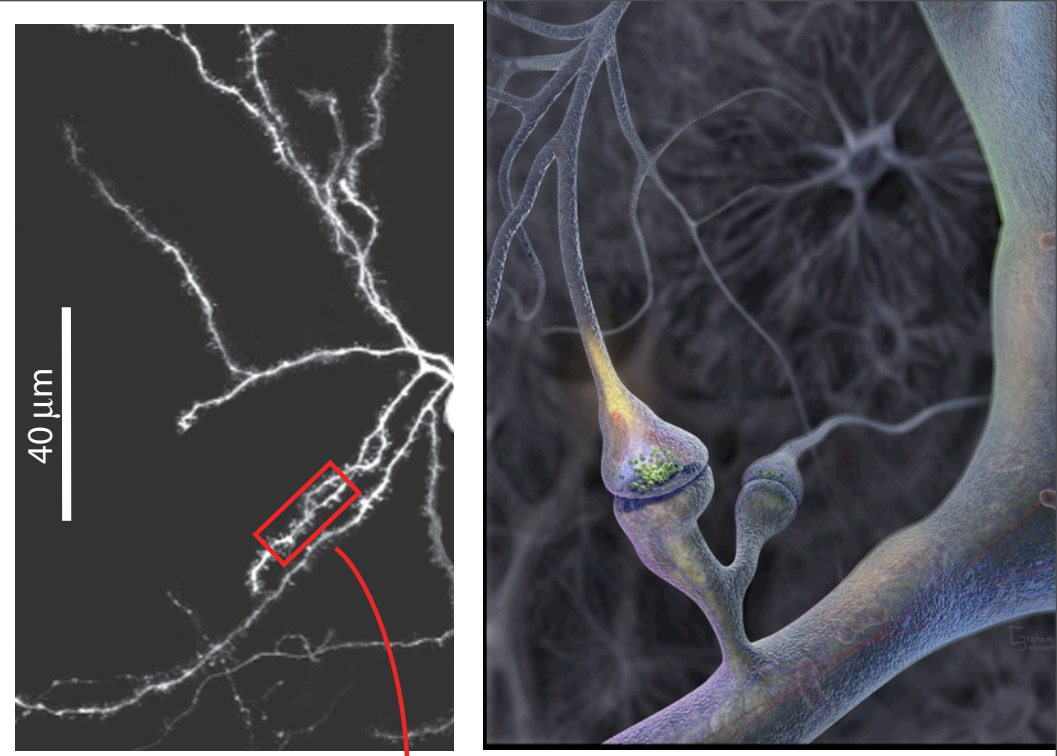

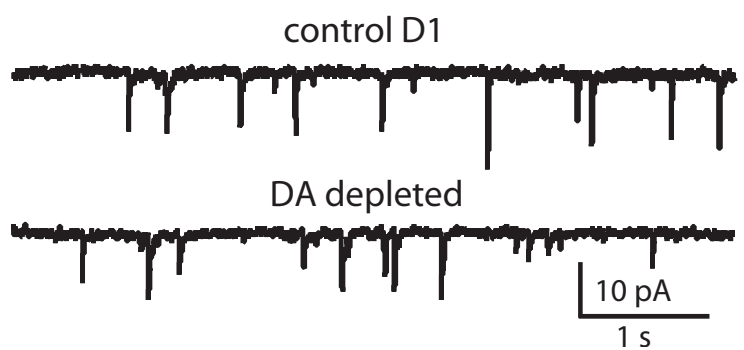

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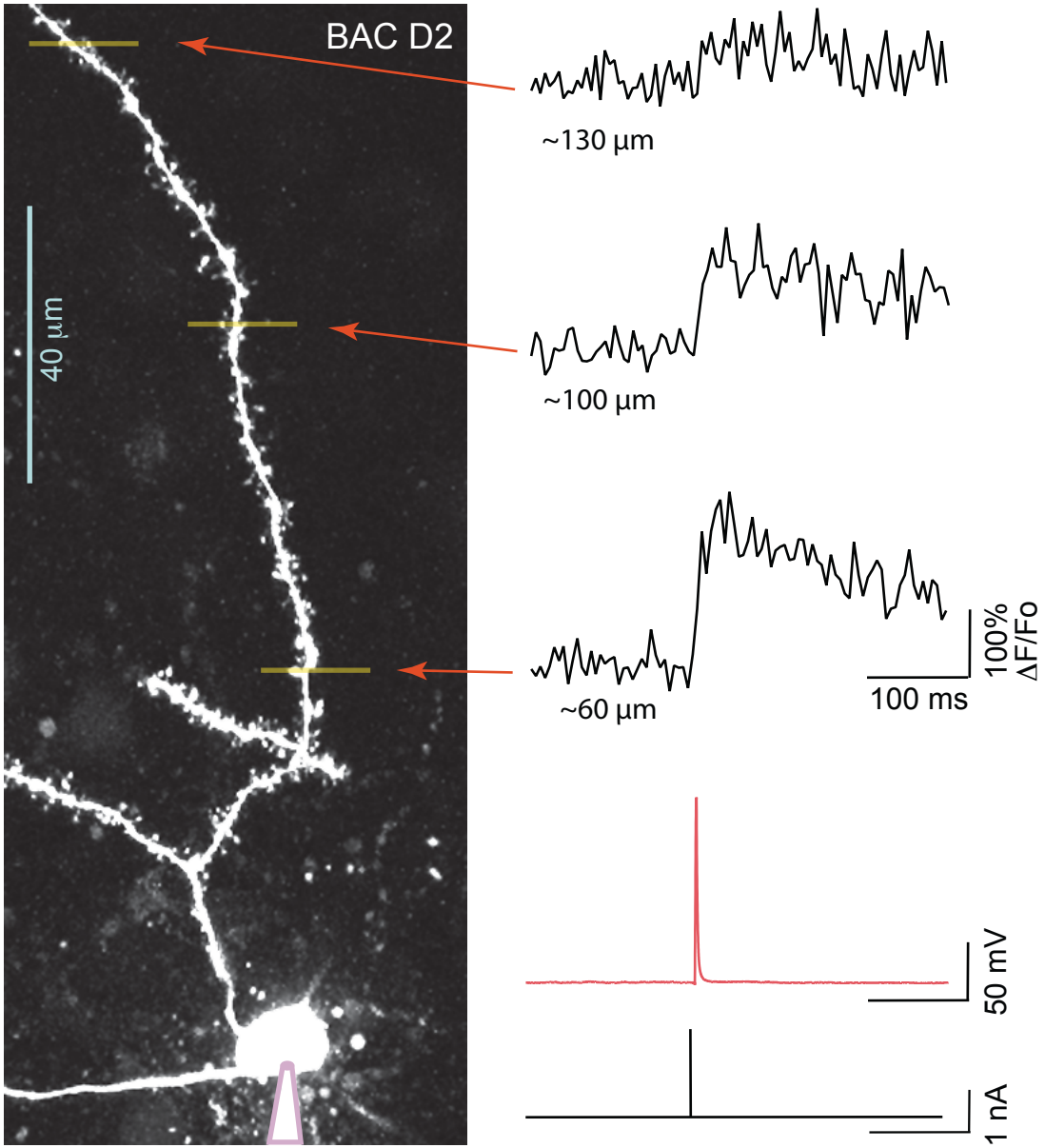
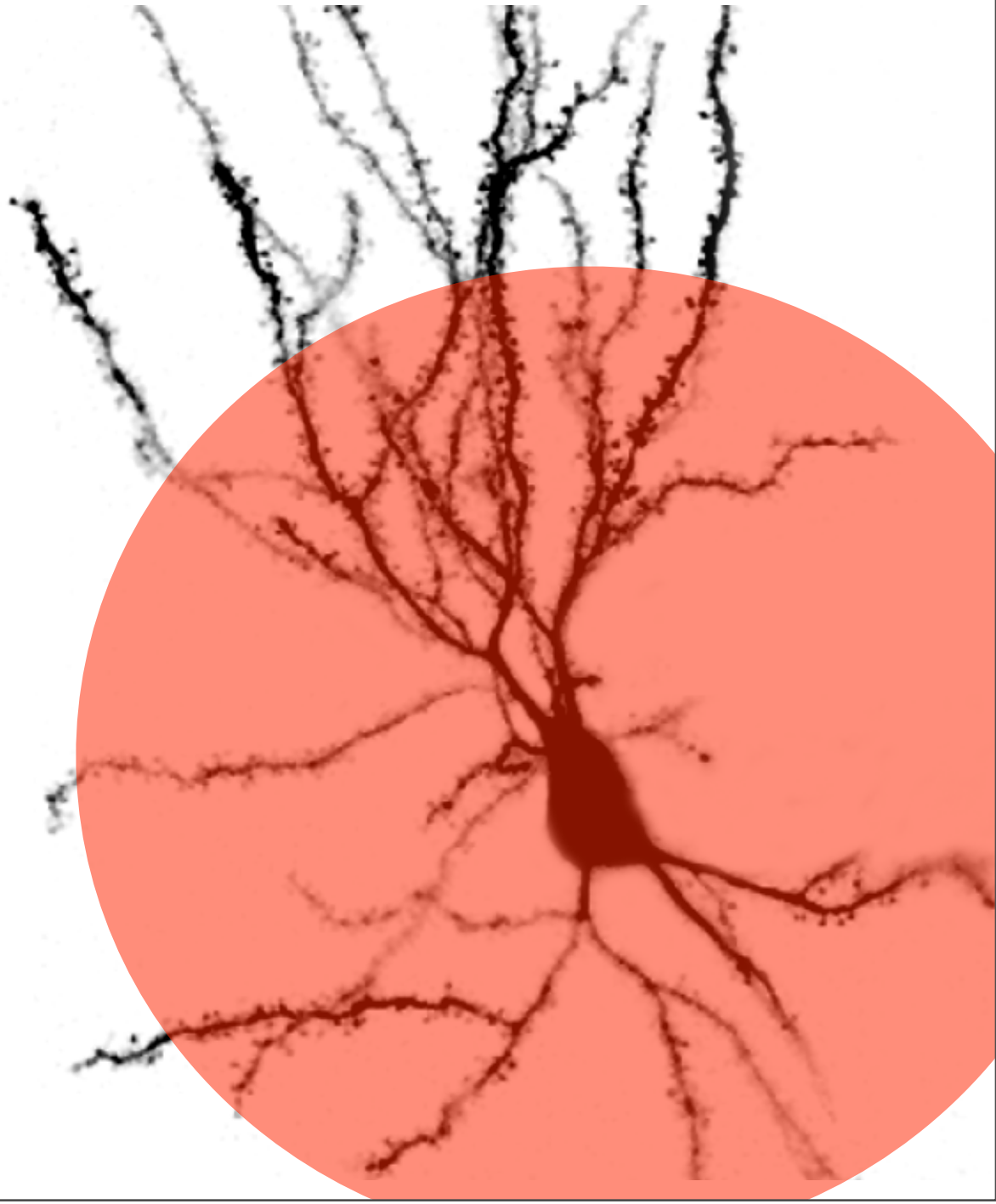


Two-photon uncaging of glutamate gives us a way of probing synapses...



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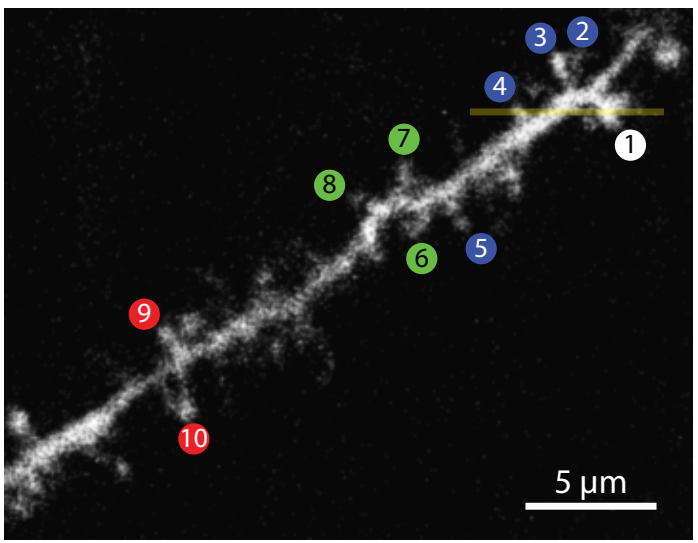
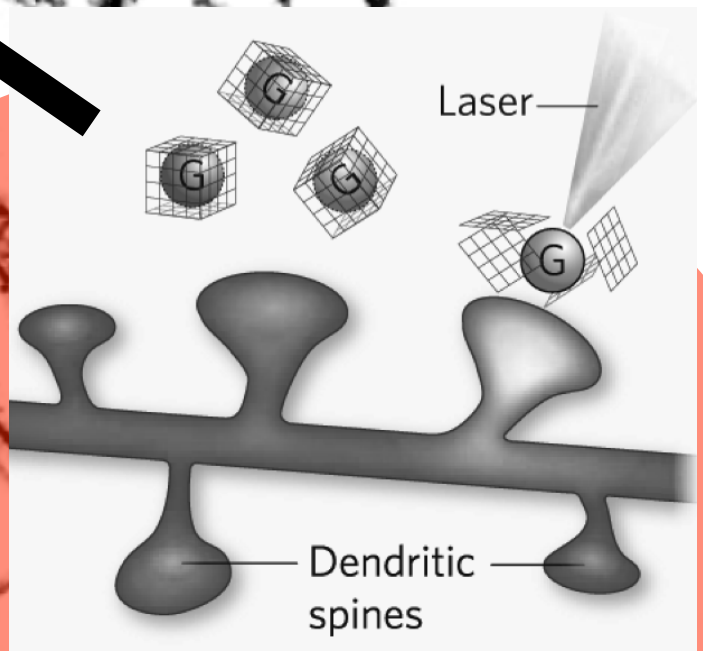
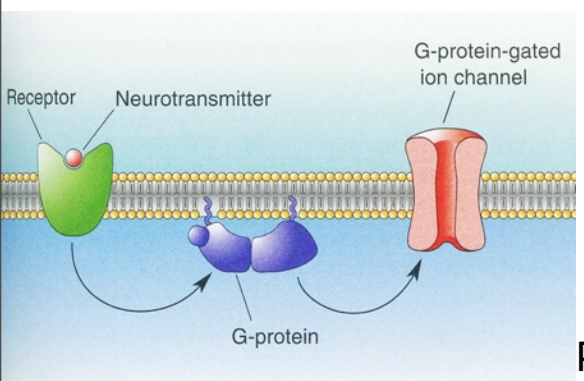
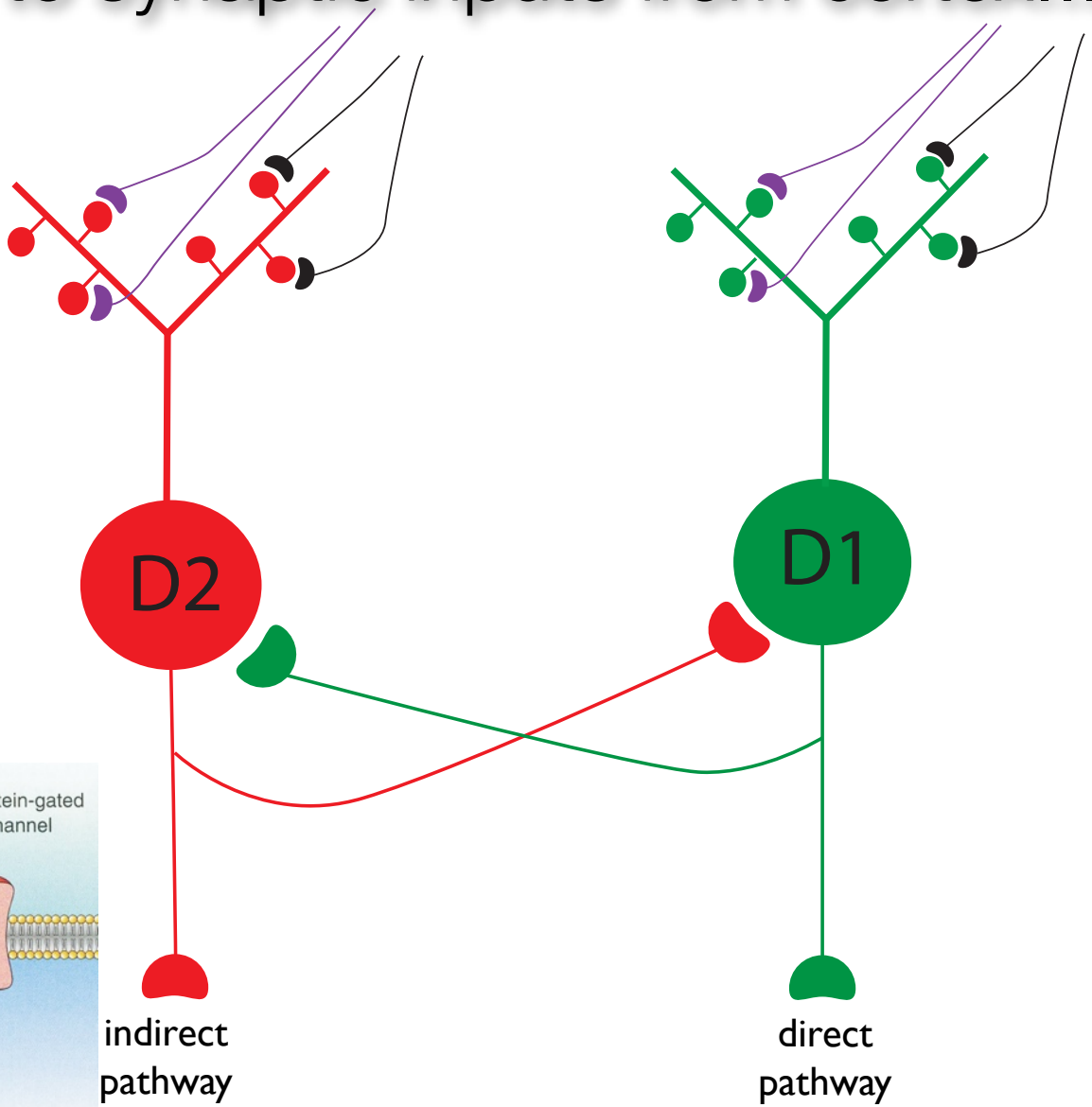




Dopamine alters intrinsic excitability and the response to synaptic inputs from cortex...





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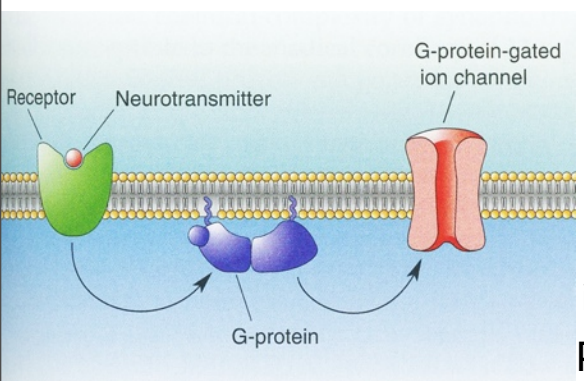

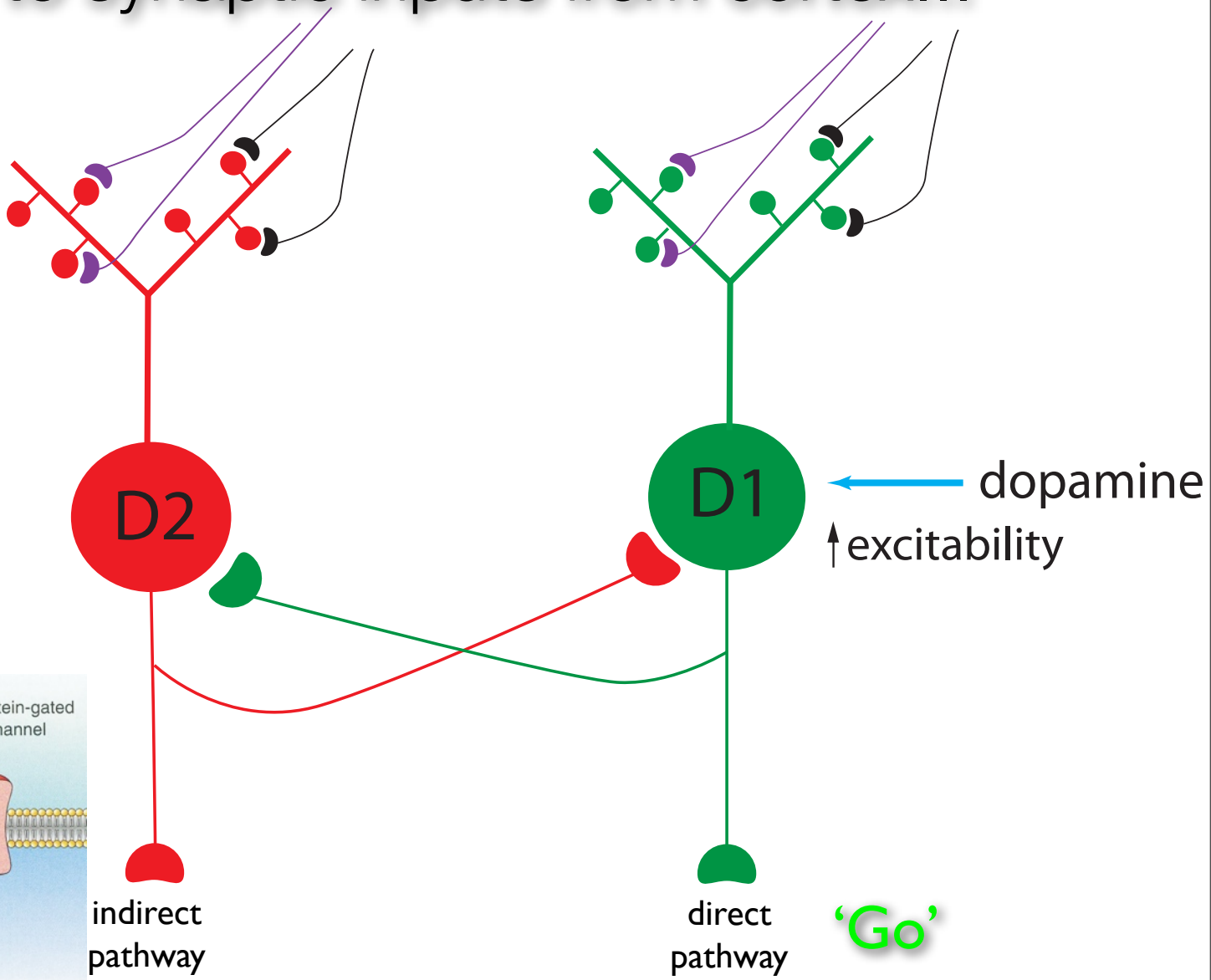

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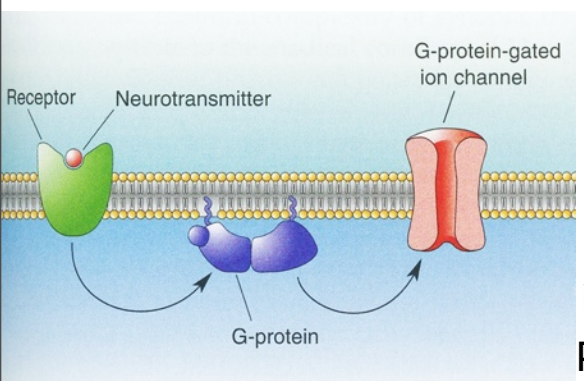

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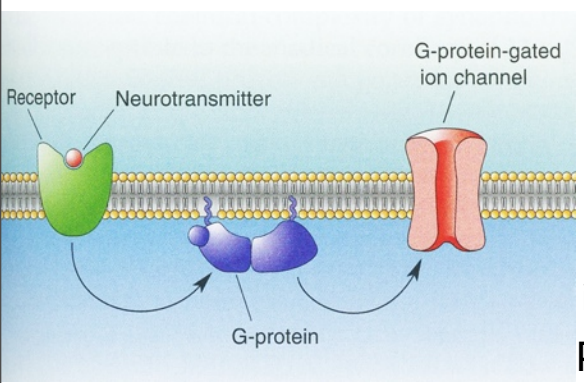

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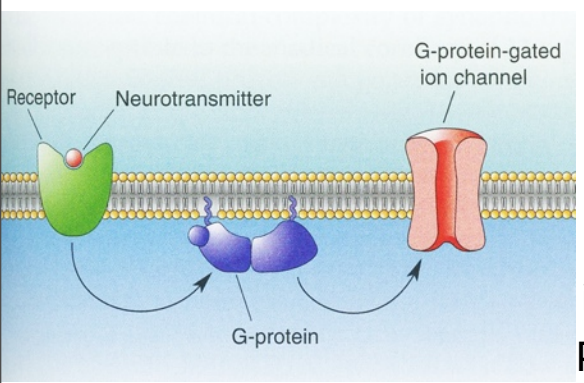
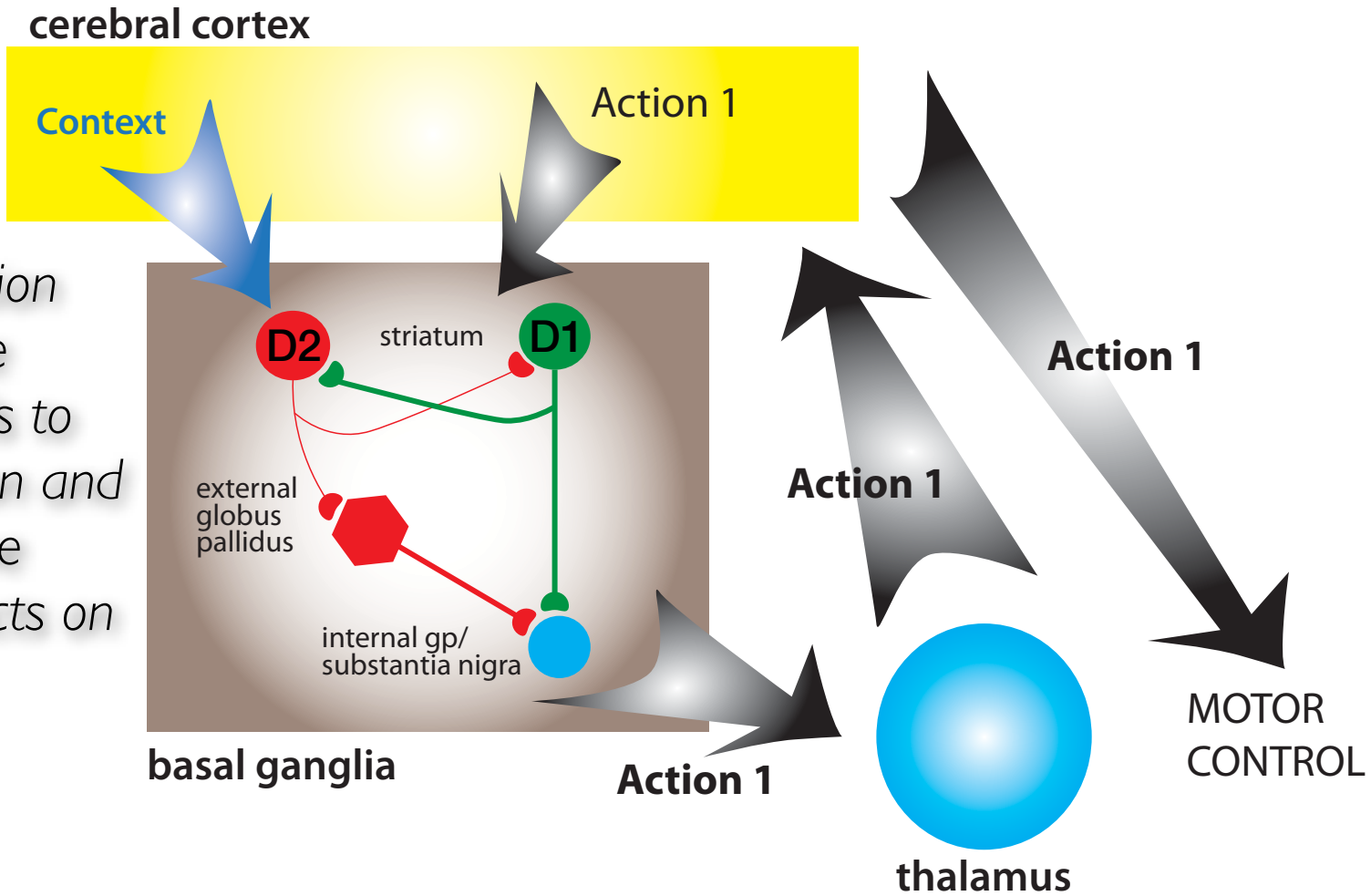


Dopamine alters intrinsic excitability and the response to synaptic inputs from cortex...

Basal ganglia control circuits

What should I do?

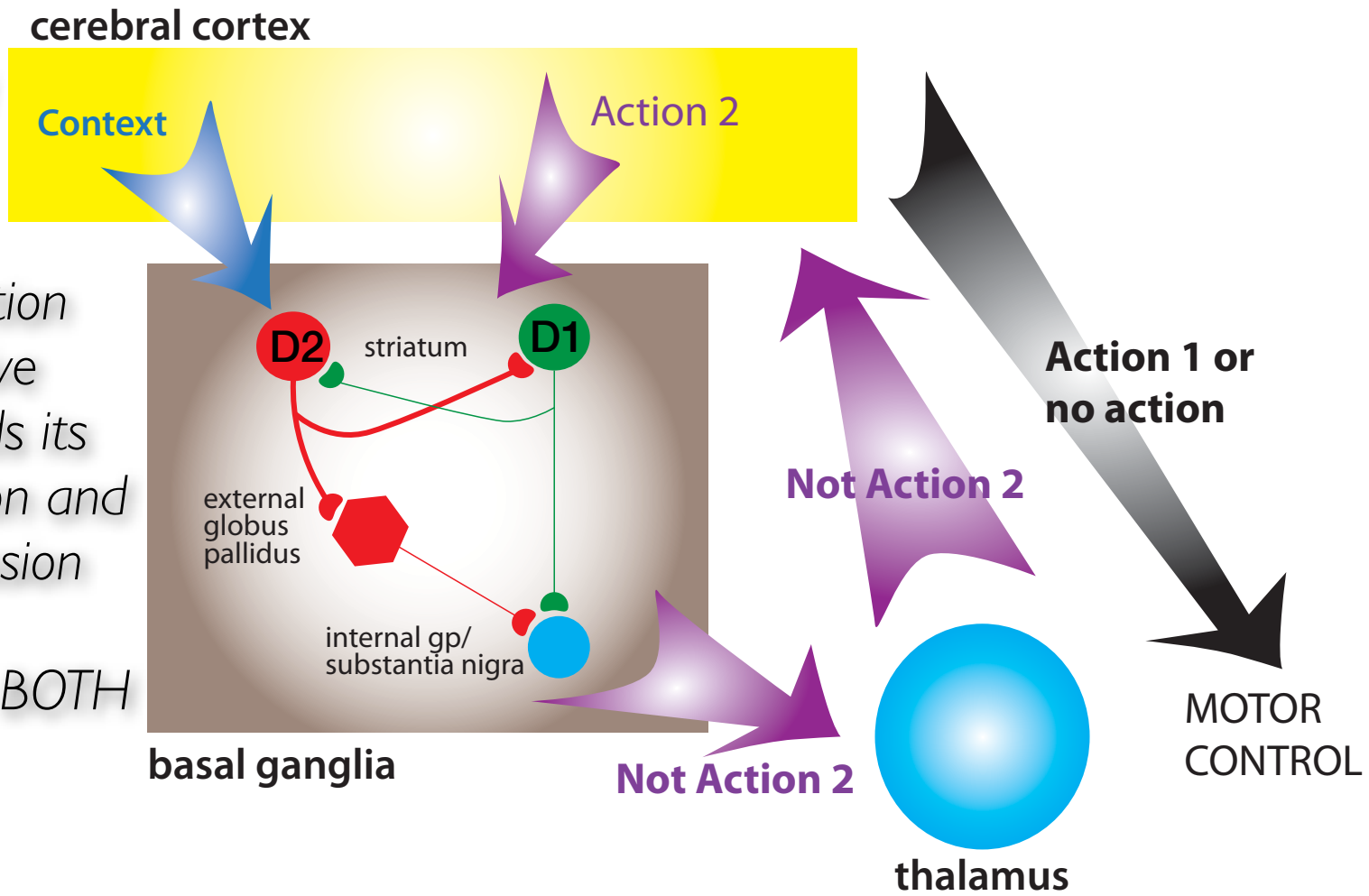
Pairing an action with a positive outcome leads to its continuation and selection in the future by effects on BOTH pathways



Basal ganglia control circuits

What should I do?

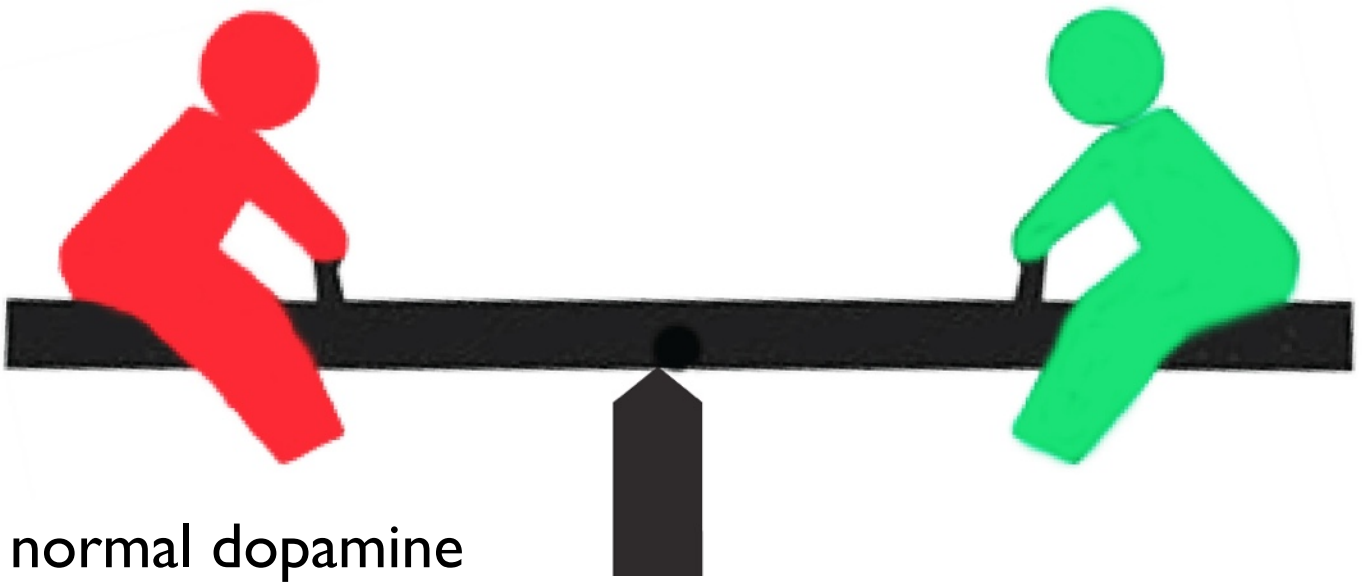
Pairing an action with a negative outcome leads its discontinuation and to its suppression in the future by effects on BOTH pathways



These two pathways can be viewed as ‘stop’ and ‘go’ circuits...

indirect pathway

direct pathway



normal dopamine

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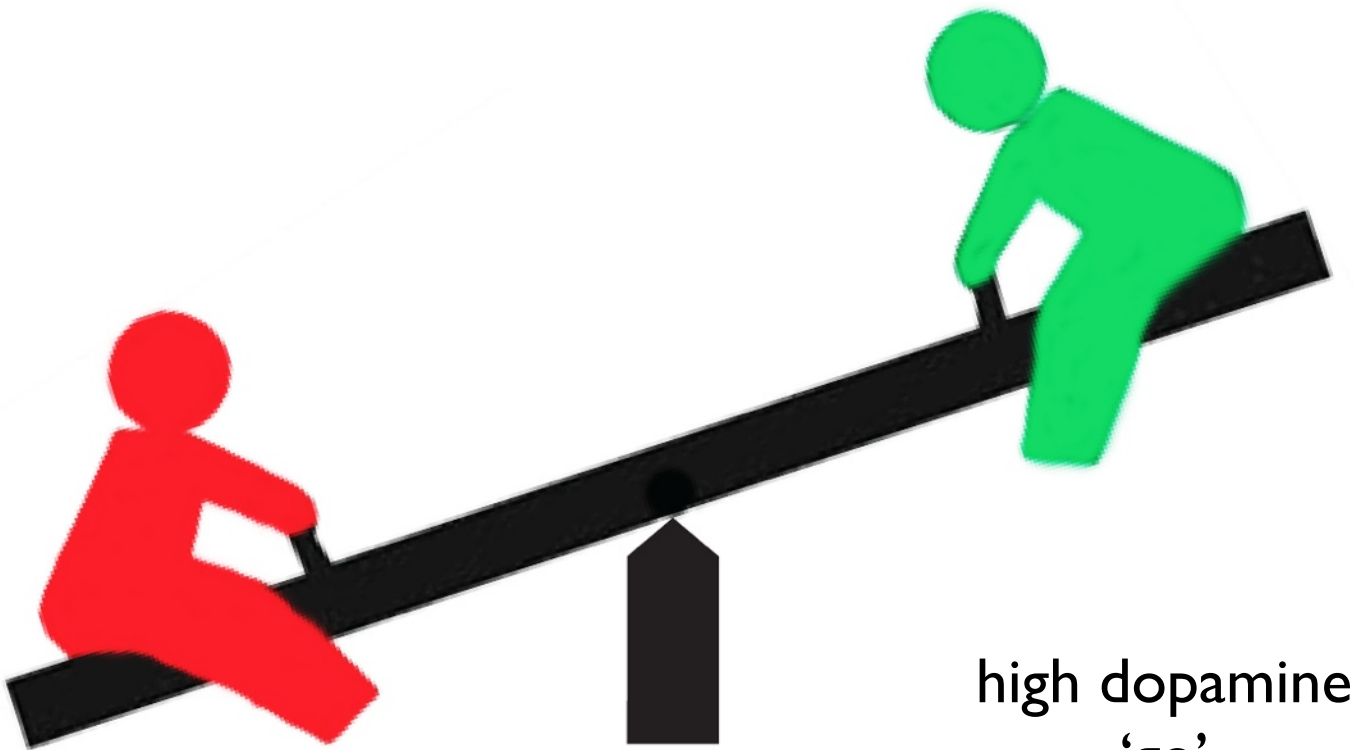
direct pathway

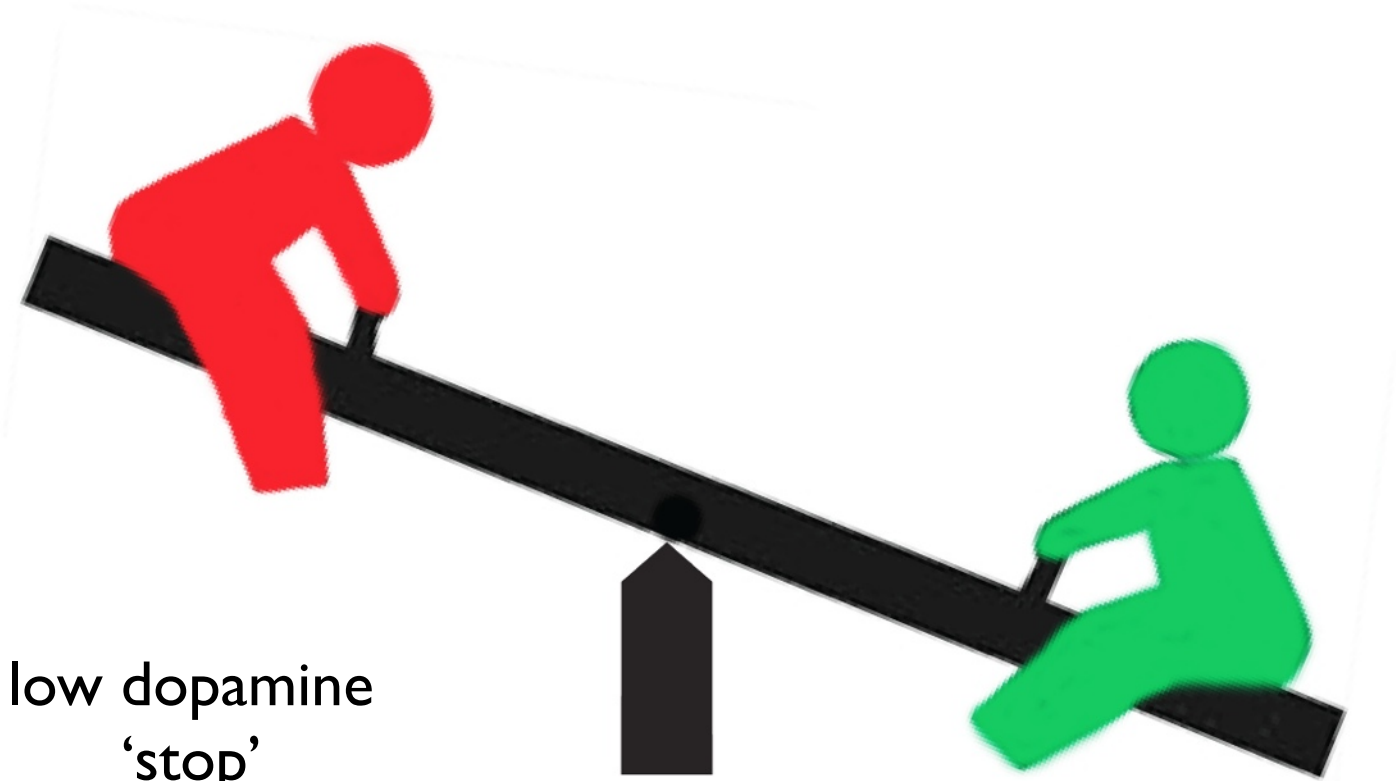


high dopamine
‘go’

These two pathways can be viewed as ‘stop’ and ‘go’ circuits...

indirect pathway

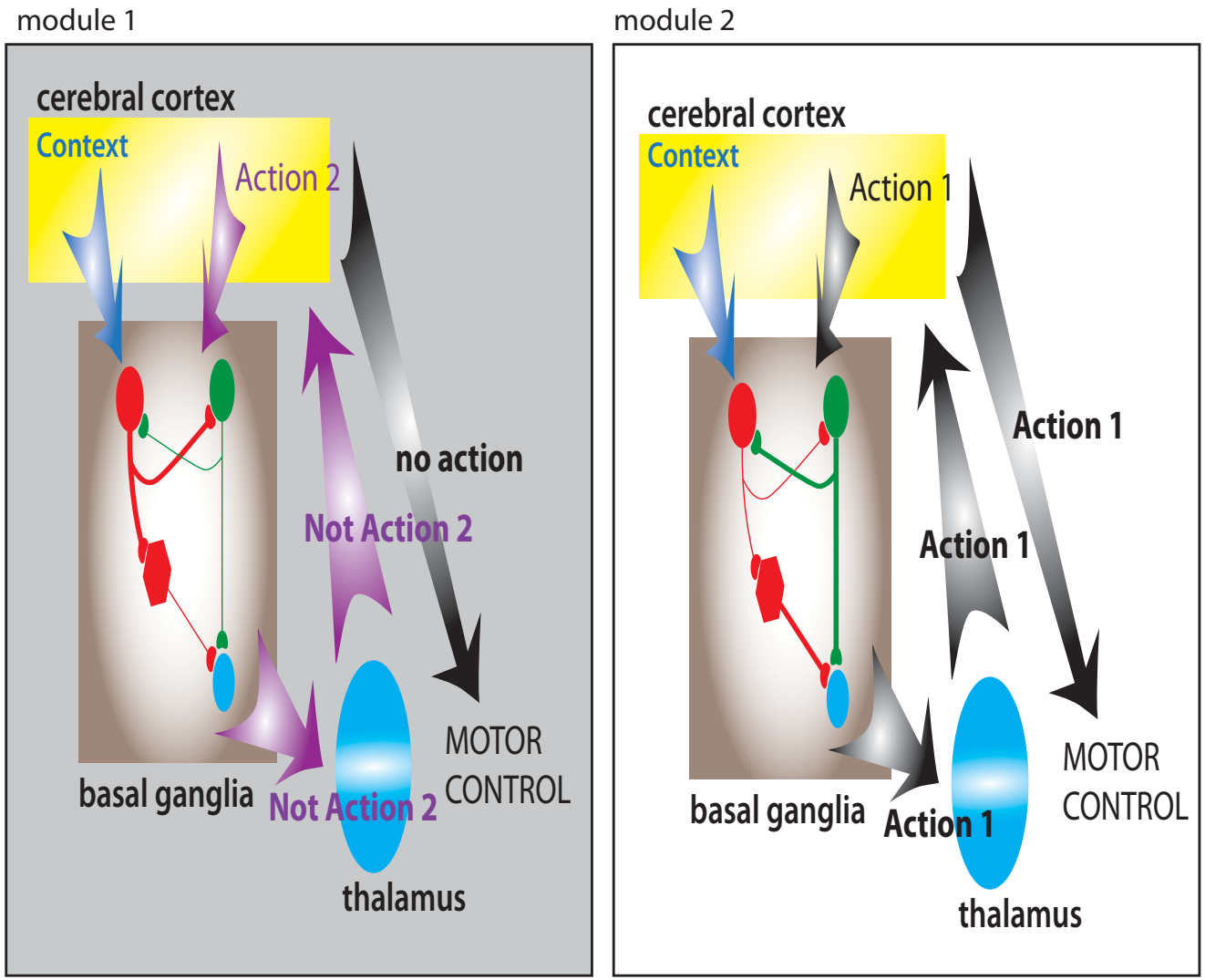
direct pathway



low dopamine
‘stop’

Basal ganglia control circuits

Control circuits or modules might exist in parallel to regulate discrete actions



These same networks are replicated to allow dopamine to control not just movement, but thought and emotion...

Summary to this point:

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- ✓ The basal ganglia helps the cerebral cortex choose what to do or not to do at any moment in time.

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Summary to this point:

- ✓ The basal ganglia helps the cerebral cortex choose what to do or not to do at any moment in time.
- ✓ Dopamine plays a key role in this process by providing feedback about whether actions are producing good or bad outcomes.
- ✓ There are two basal ganglia sub-circuits that respond differently to dopamine: *one that promotes action, the other that stops action.*
- ✓ This basic circuit is repeated throughout the frontal cortices to control cognition and emotion.

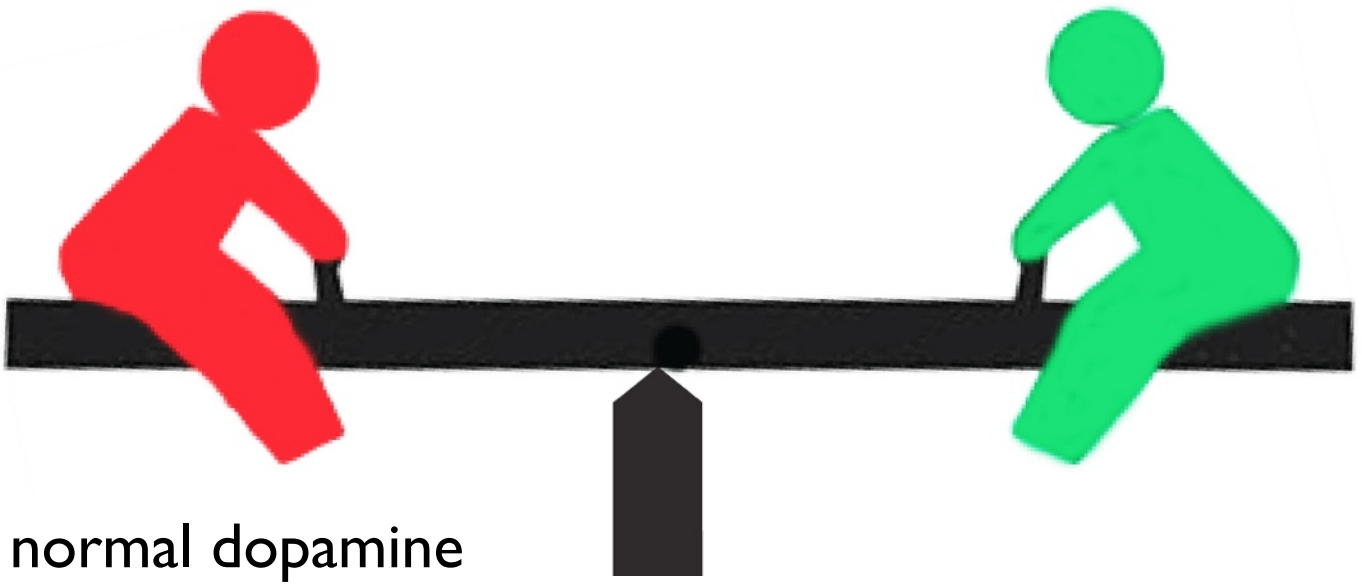
Alterations in dopamine function within these modules has been linked to a wide variety of disorders including drug abuse, schizophrenia, dystonia, Huntington's disease, and Parkinson's disease...

These diseases can be grouped into hyperkinetic and hypokinetic categories. Each is thought to reflect an imbalance in striatal function...

With normal dopamine levels the pathways are balanced...

indirect pathway

direct pathway



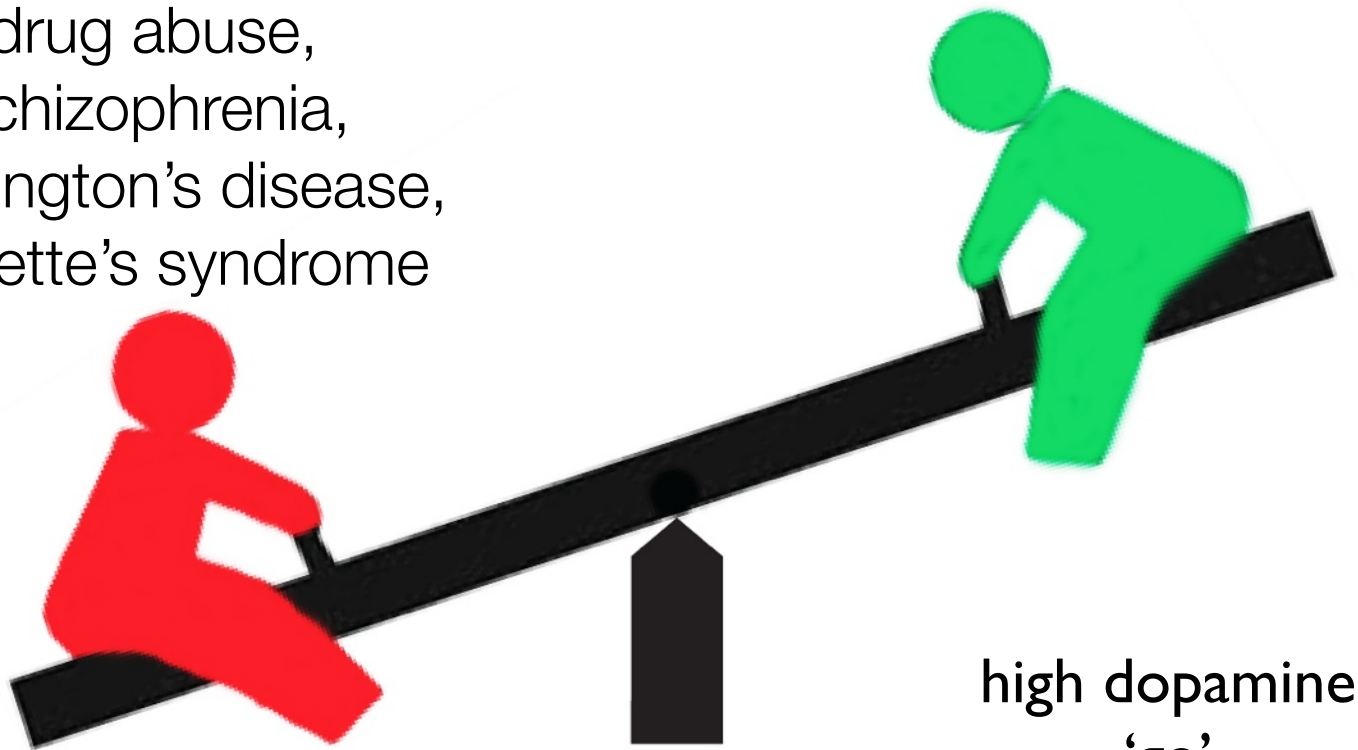
normal dopamine

Hyperkinetic disorders are associated with elevated dopamine release or function...

indirect pathway

direct pathway

drug abuse,
schizophrenia,
Huntington's disease,
Tourette's syndrome

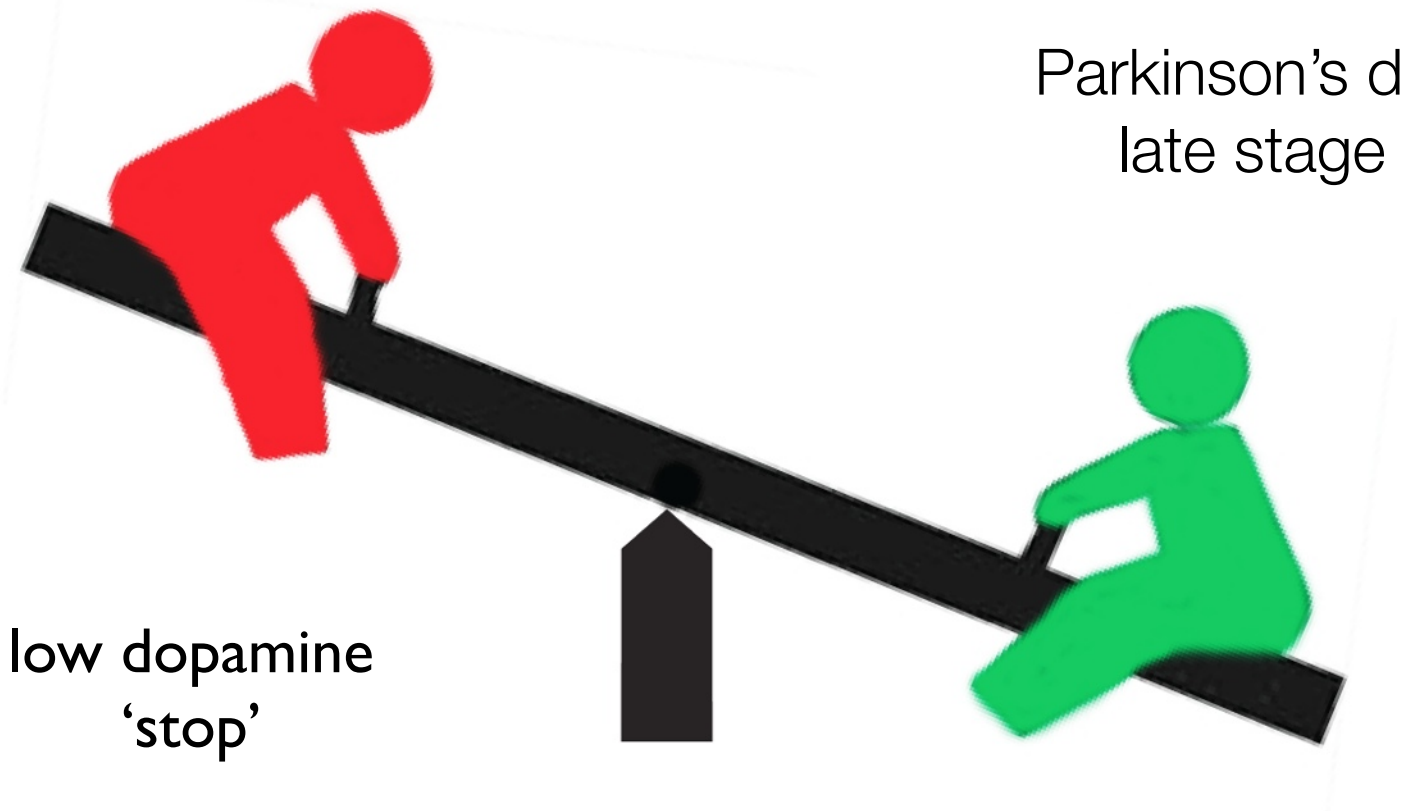


high dopamine
'go'

Hypokinetic disorders are associated with decreased dopamine release or function...

indirect pathway

direct pathway



Parkinson's disease
late stage HD

low dopamine
'stop'

Parkinson's disease is the most prevalent hypokinetic disorder of the basal ganglia...

Parkinson's disease is a progressive, neurodegenerative disease associated with aging.

The symptoms of Parkinson's disease include tremor, rigidity, slowness of movment, difficulty initiating movement and poor postural stability.

Parkinson's disease is the second most common neurodegenerative disease in the world.

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PD has no cure

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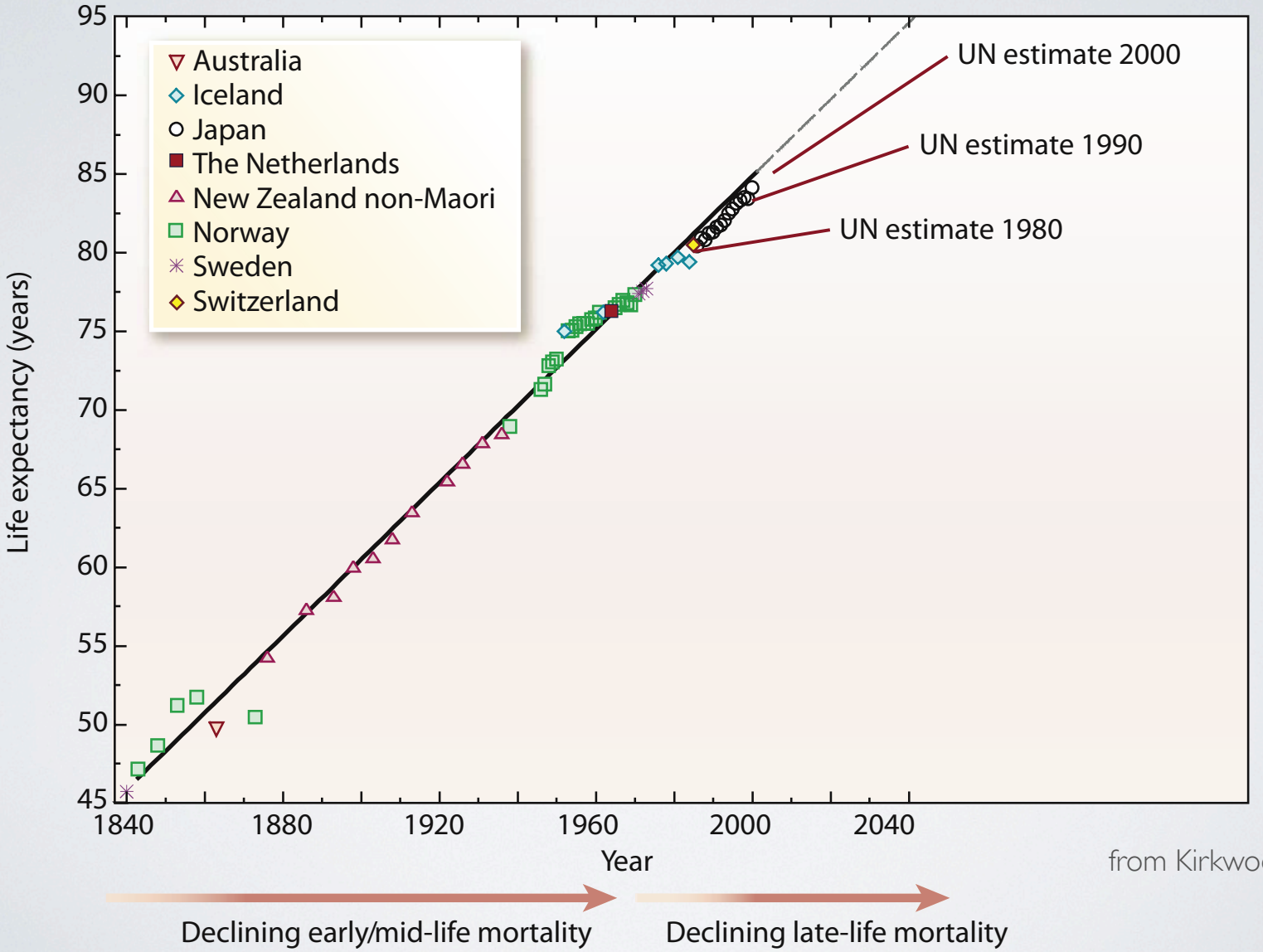
PD has no cure

Moreover, in spite of an intensive effort to identify neuroprotective agents for PD, nothing is known to slow the progression of the disease.

The strongest predictor of PD is age...



from Kirkwood, 2008

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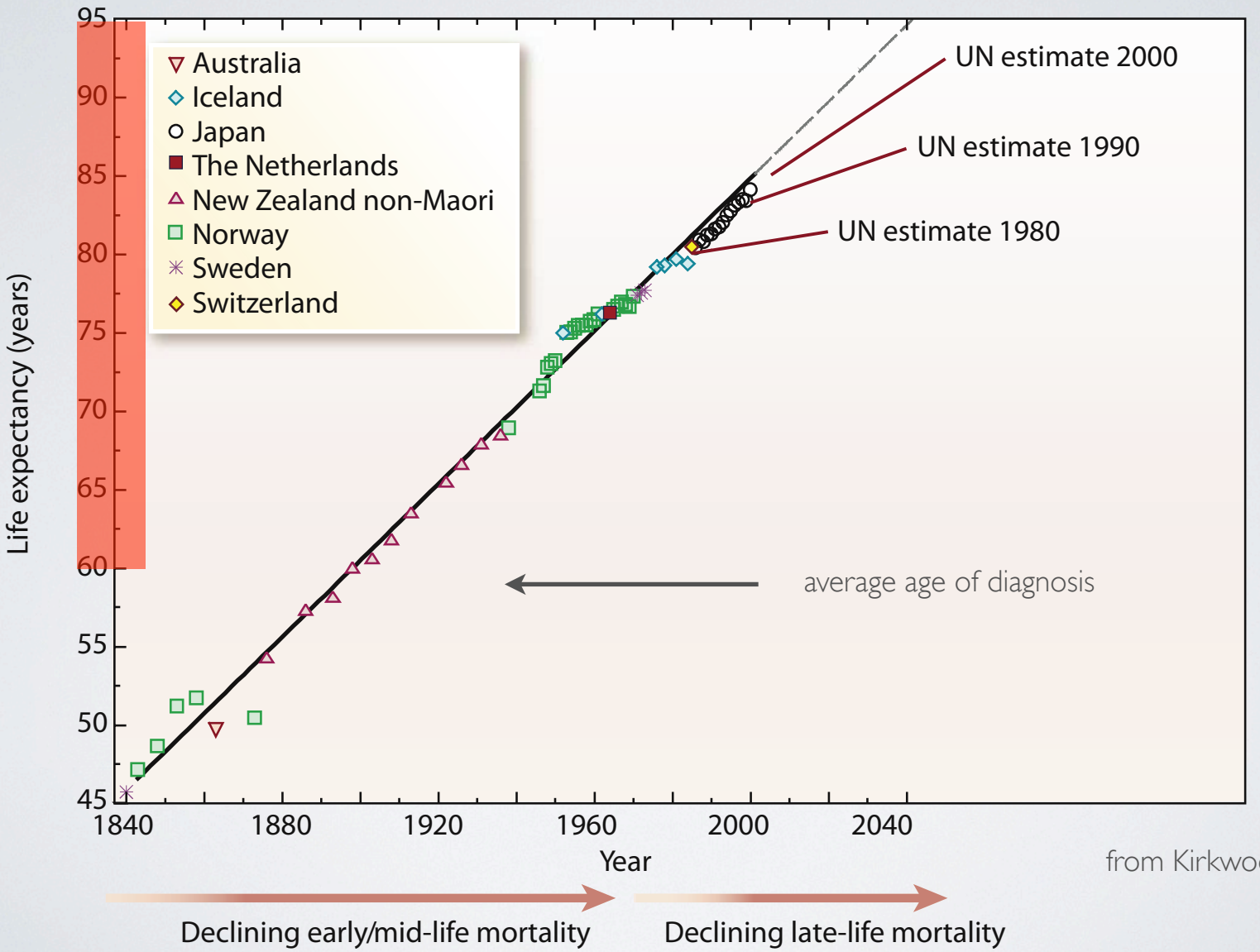
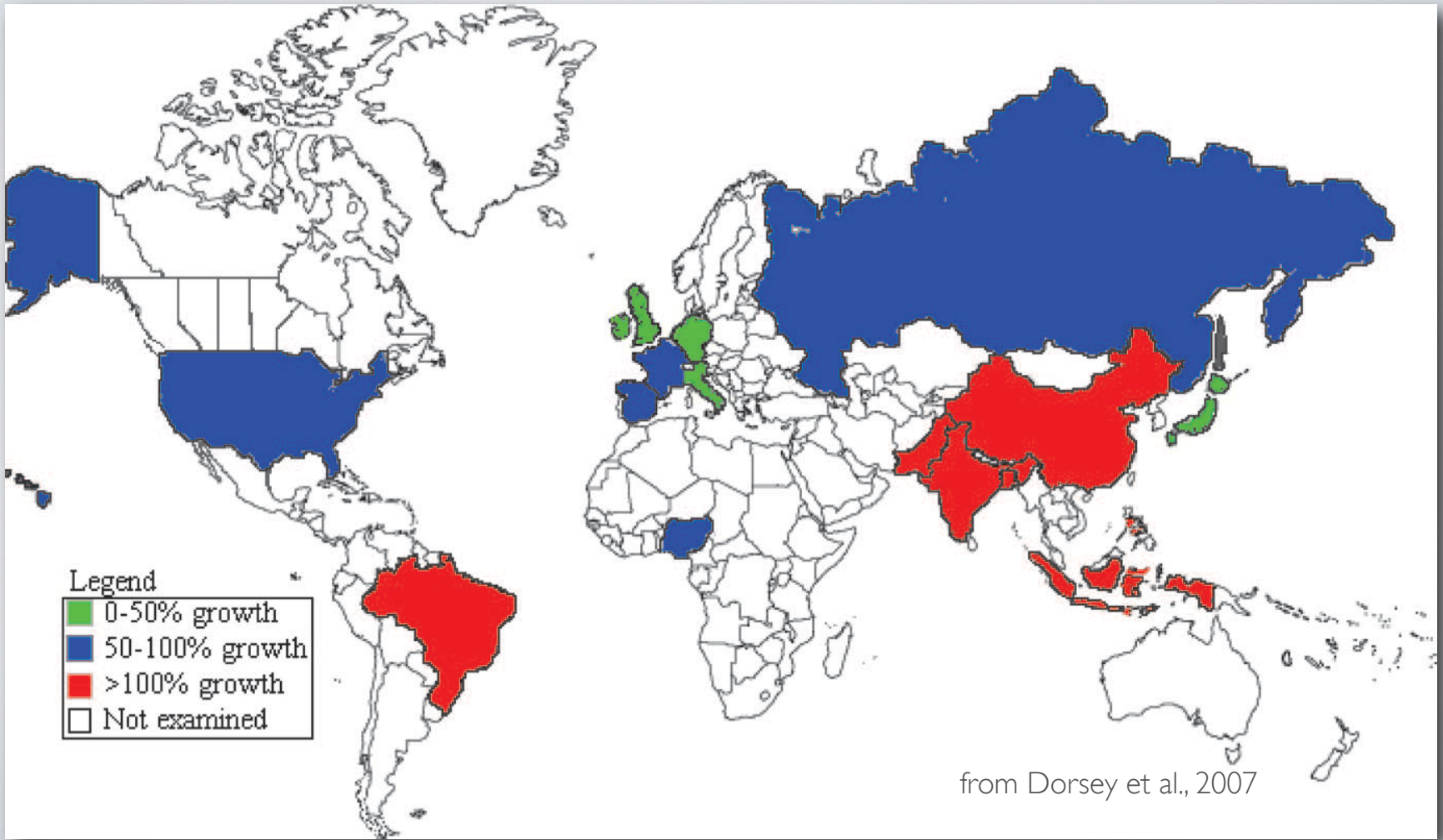


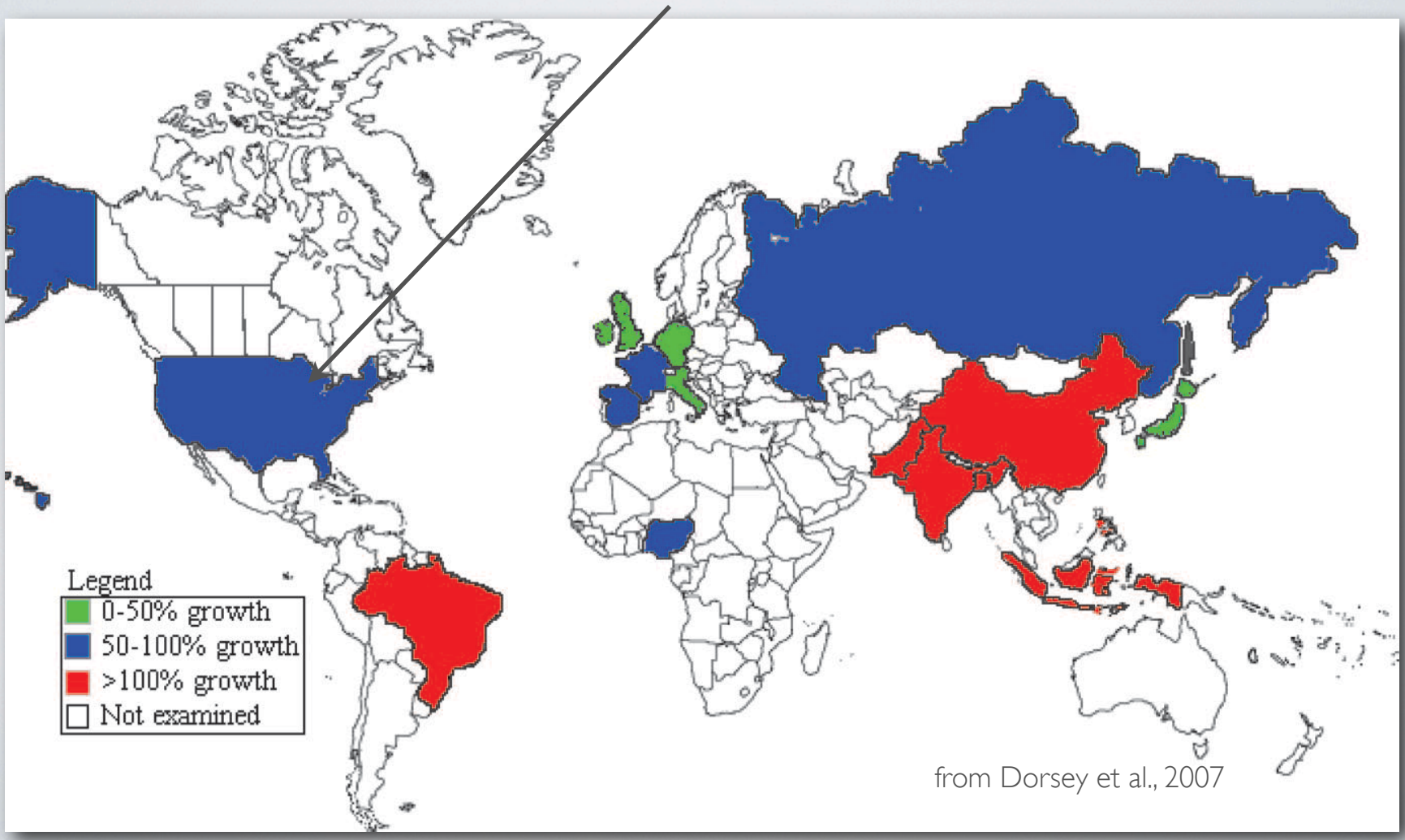
from Kirkwood, 2008

As our global population ages, the prevalence of PD is expected to dramatically increase.



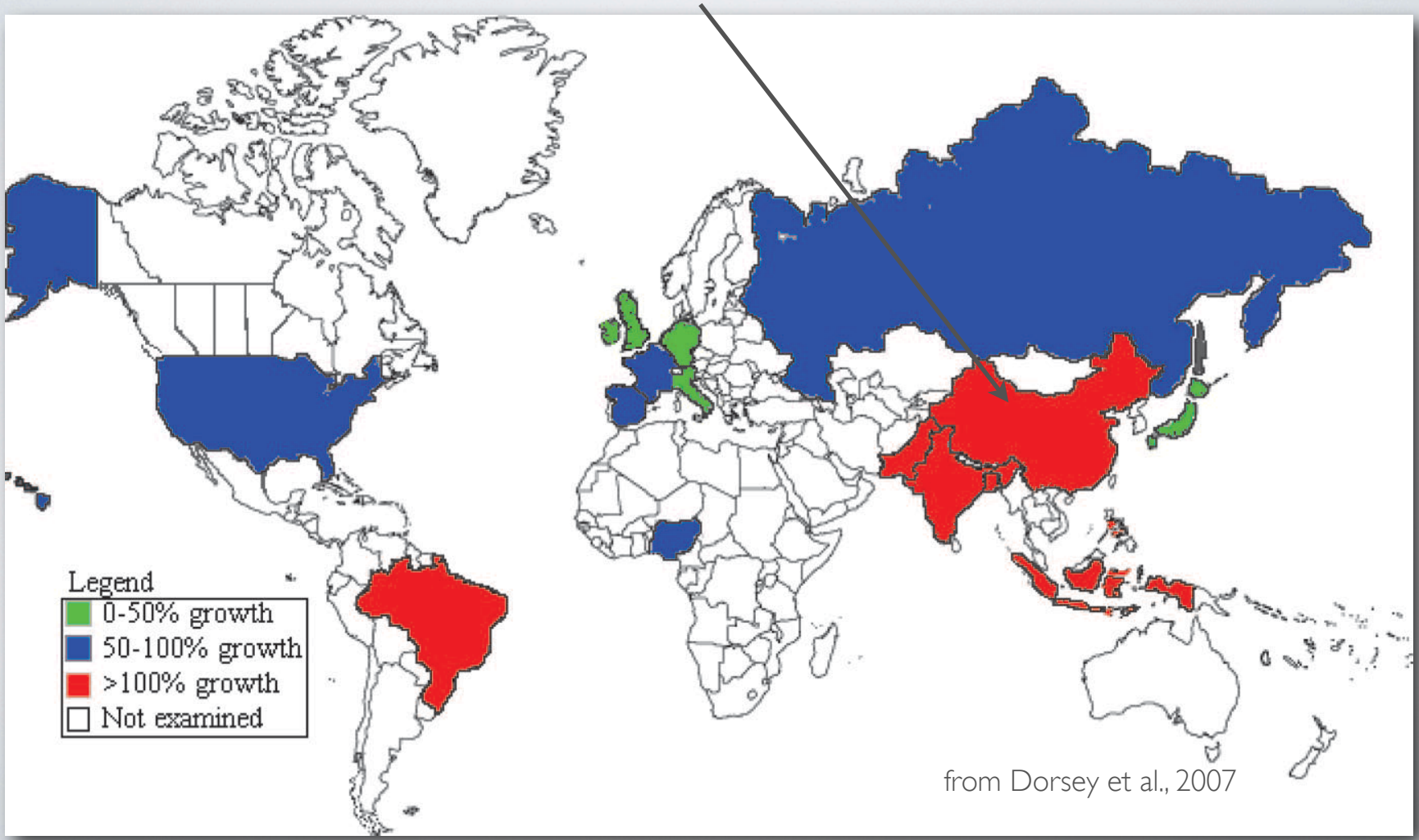
from Dorsey et al., 2007

In the next 20 years, the PD population in the U.S. is predicted to increase by nearly 100%, growing to about 2 million Americans.



from Dorsey et al., 2007

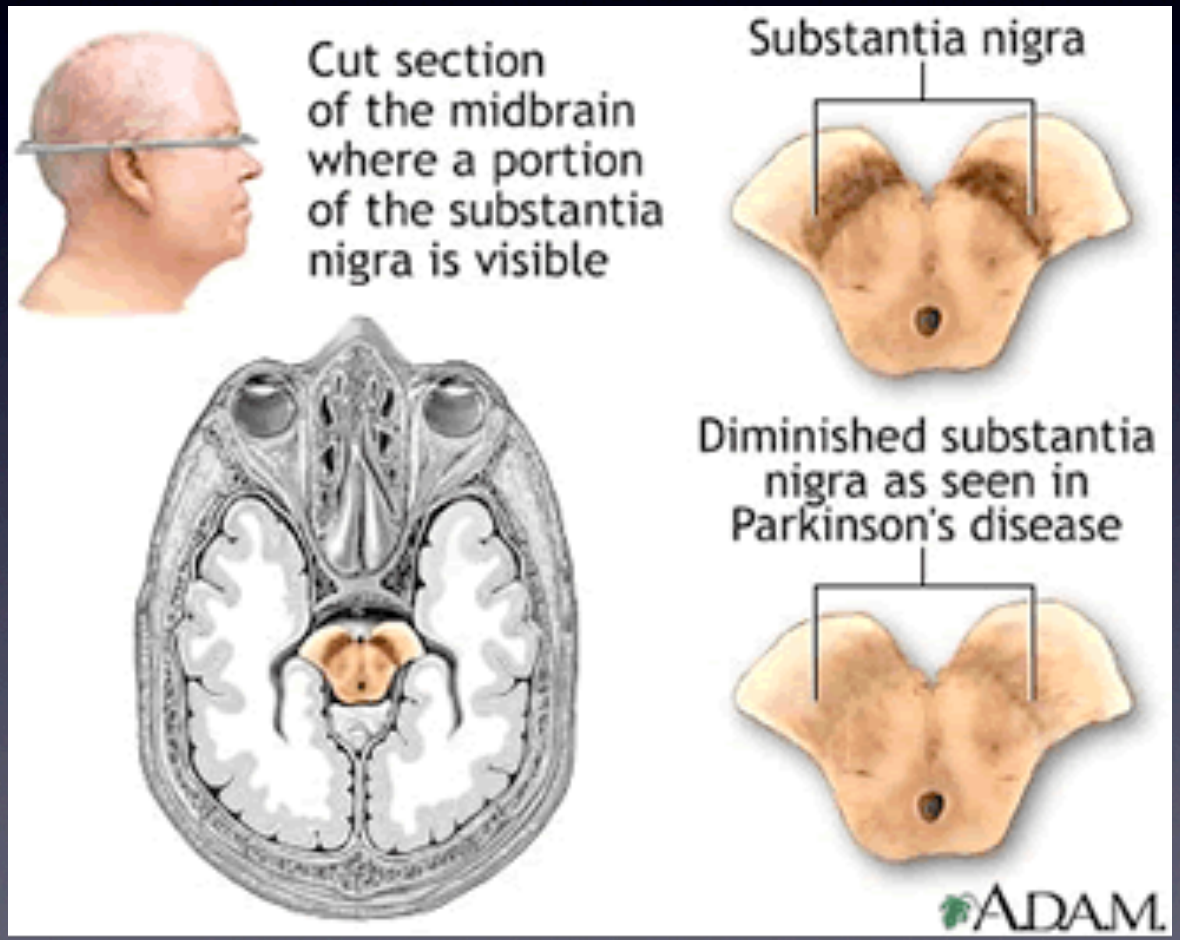
In China, the prevalence of PD is expected to rise even more, growing to nearly 5 million.



from Dorsey et al., 2007

Current healthcare costs associated with PD range from $25-50 billion/ year...

The motor symptoms of Parkinson's disease are attributable to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc).



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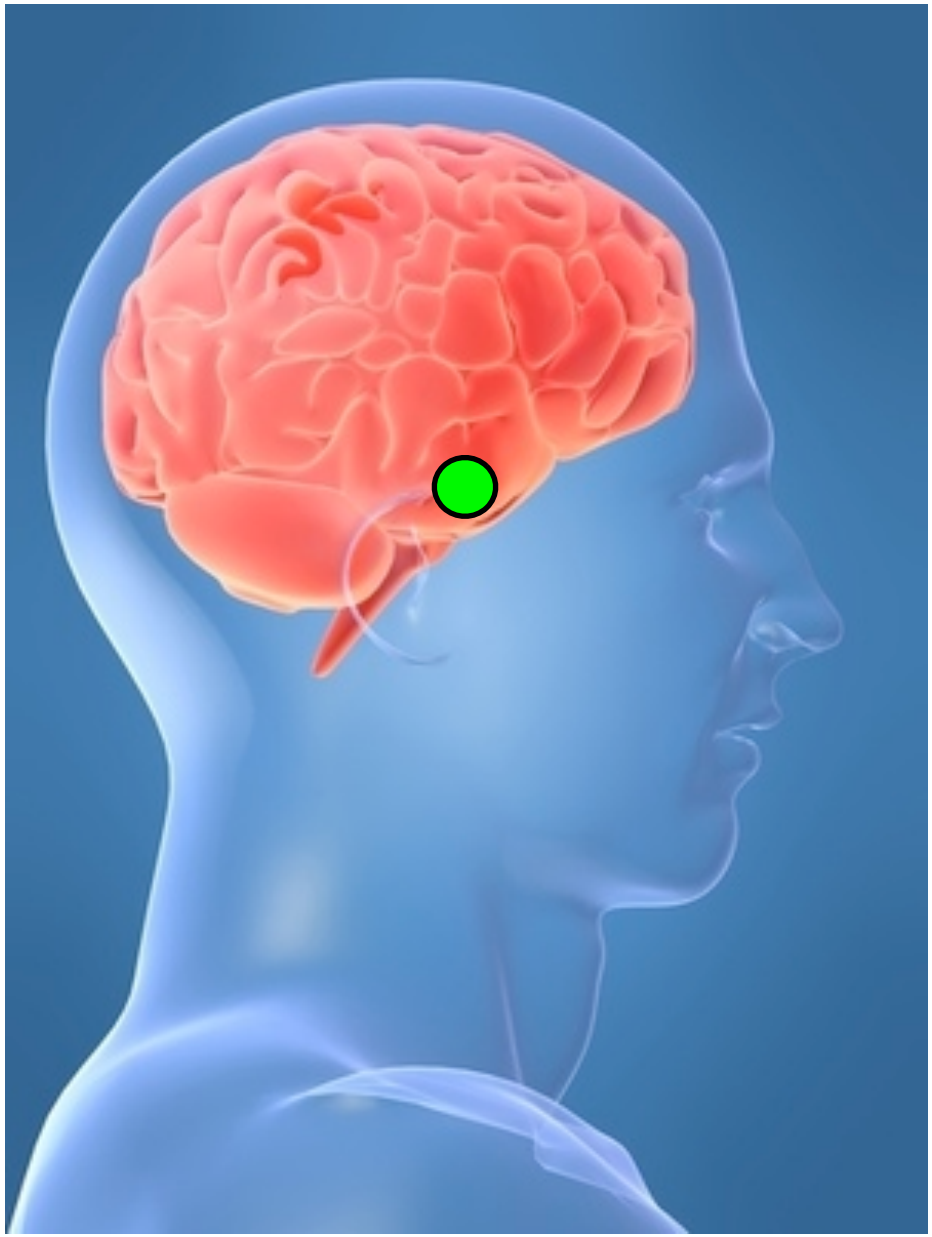
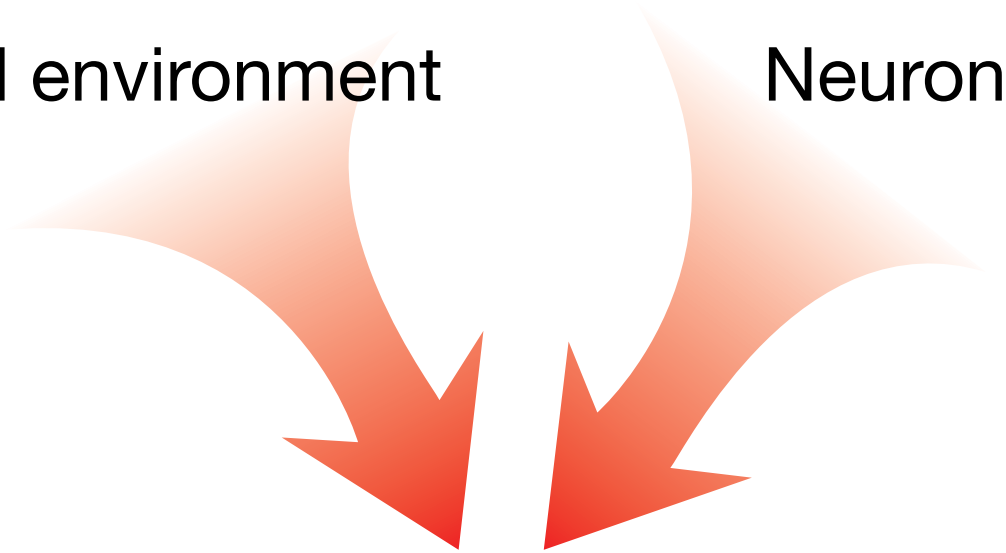


What makes this small group of neurons vulnerable?

The pattern of cell loss in PD must be governed by the interaction between genes, environment and design factors...

Genes and environment

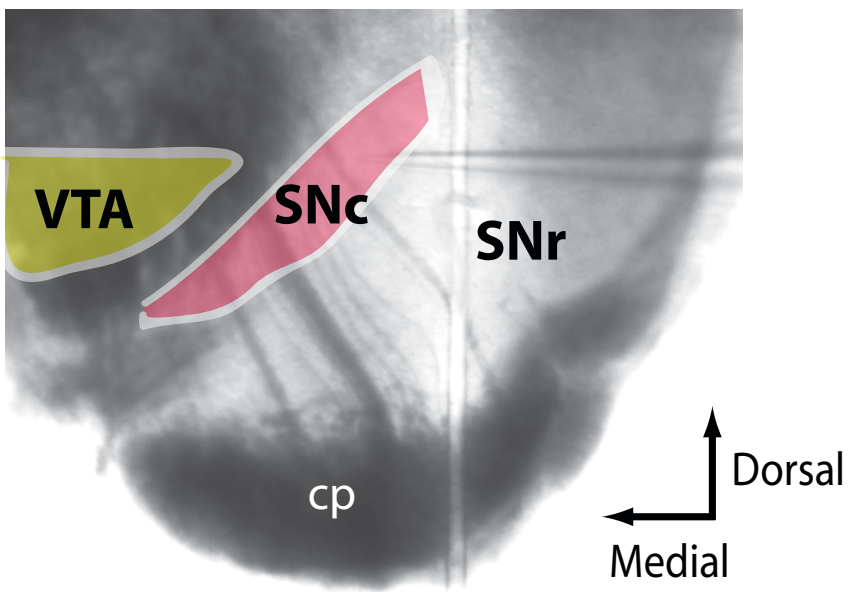
Neuronal design



Pathogenesis

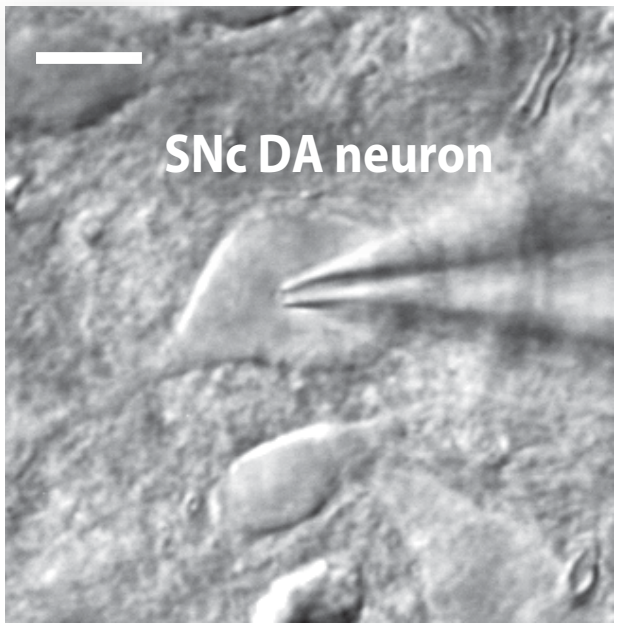
What are the neuronal design factors that underlie vulnerability?

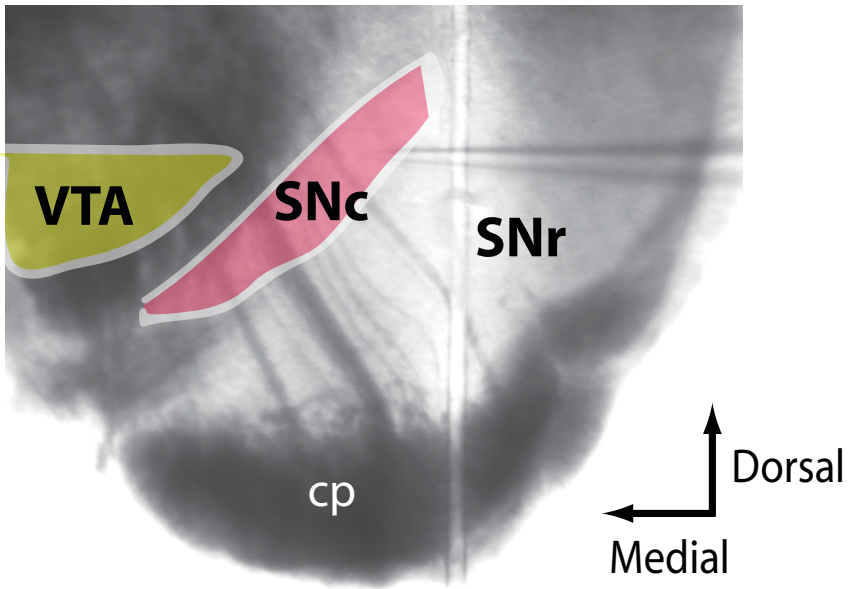
Vulnerable dopaminergic neurons are slow, autonomous pacemakers:



Vulnerable dopaminergic neurons are slow, autonomous pacemakers:

IR-DIC





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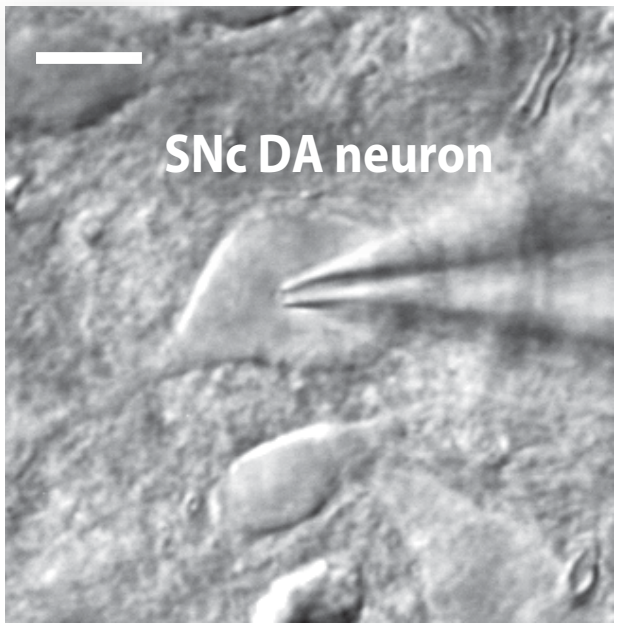
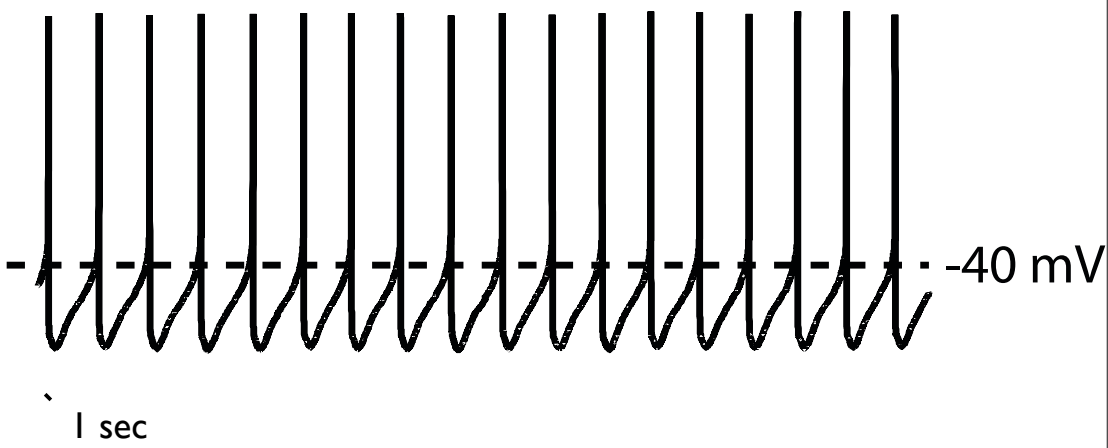
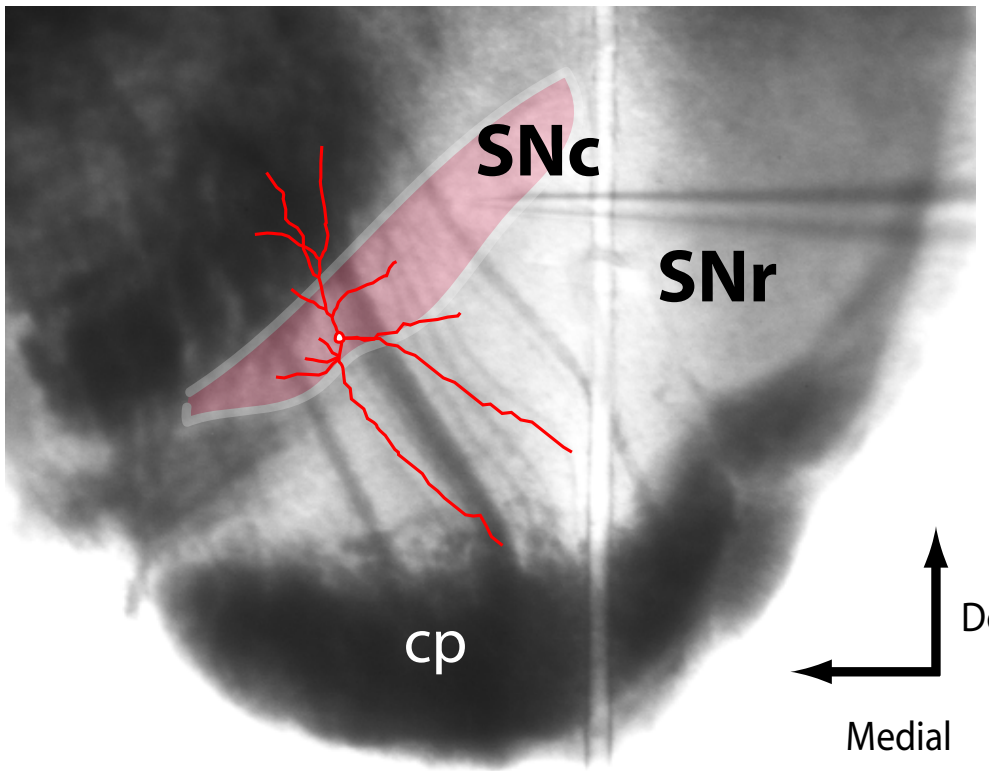
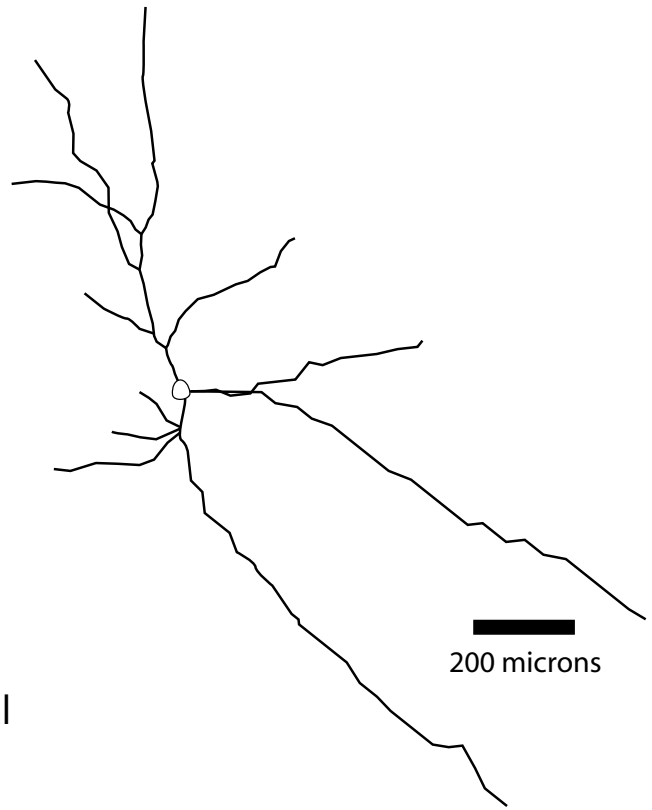




Pacemaking in SNc DA neurons triggers unusual fluctuations in both dendritic and somatic calcium concentration....





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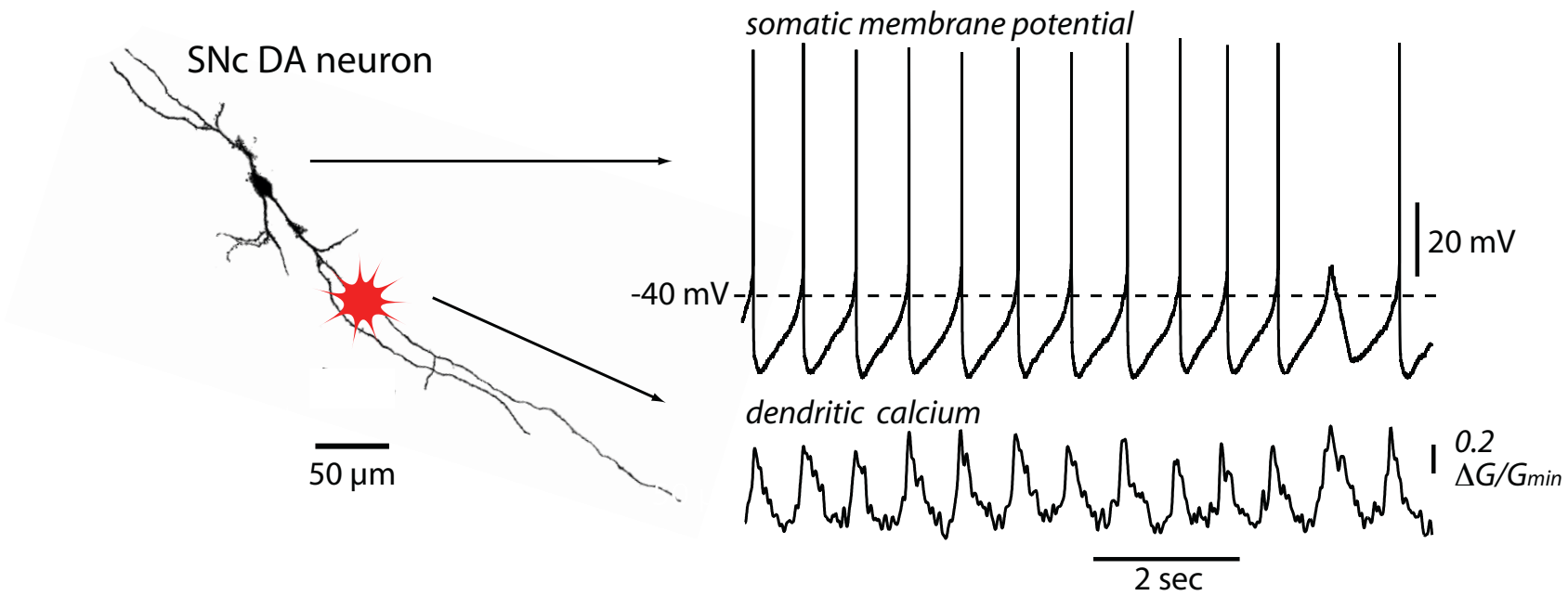
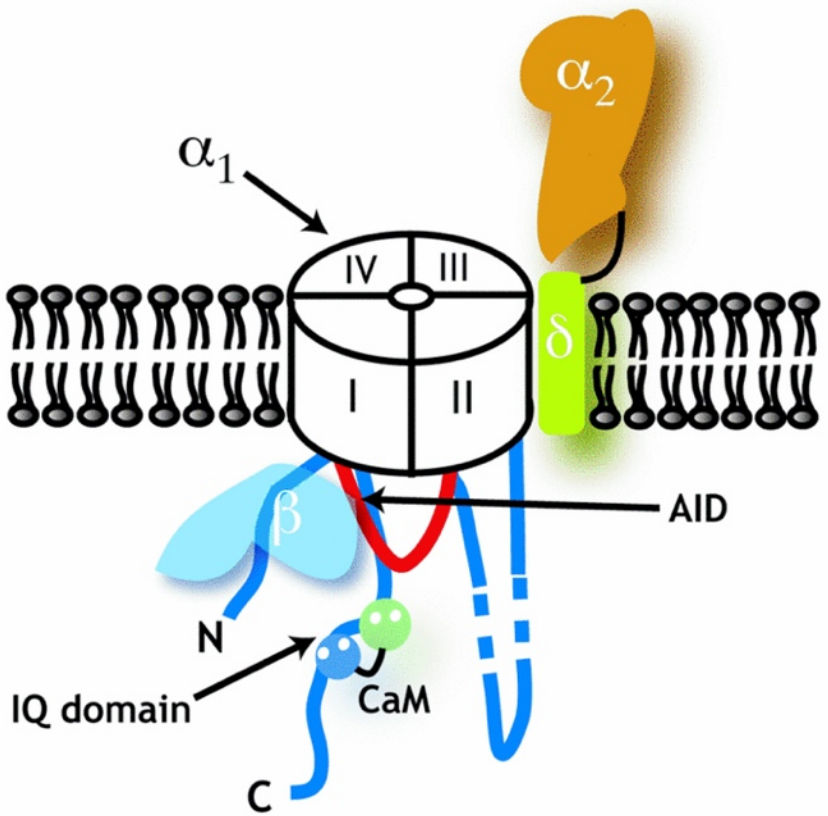


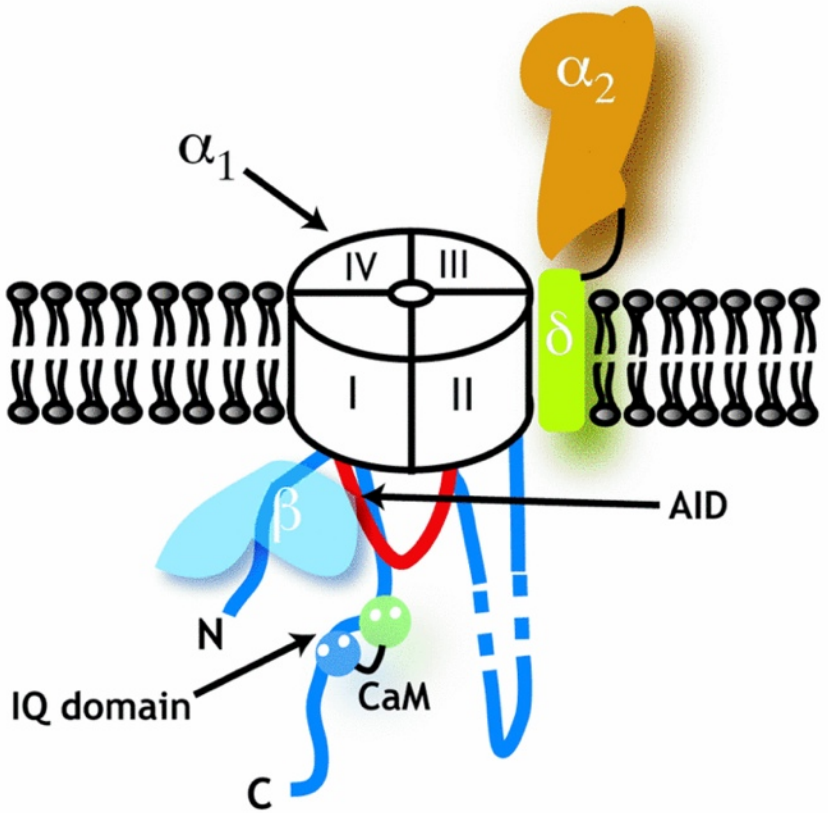
The calcium channel underlying these oscillations has a distinctive Cav1.3 pore.



Cav1.3 channels constitute 10% of all L-type channels in the brain and less that 3% of all voltage-dependent channels making it an attractive target..

Among the dihydropyridines, **isradipine** has the highest affinity for Cav1.3 channels

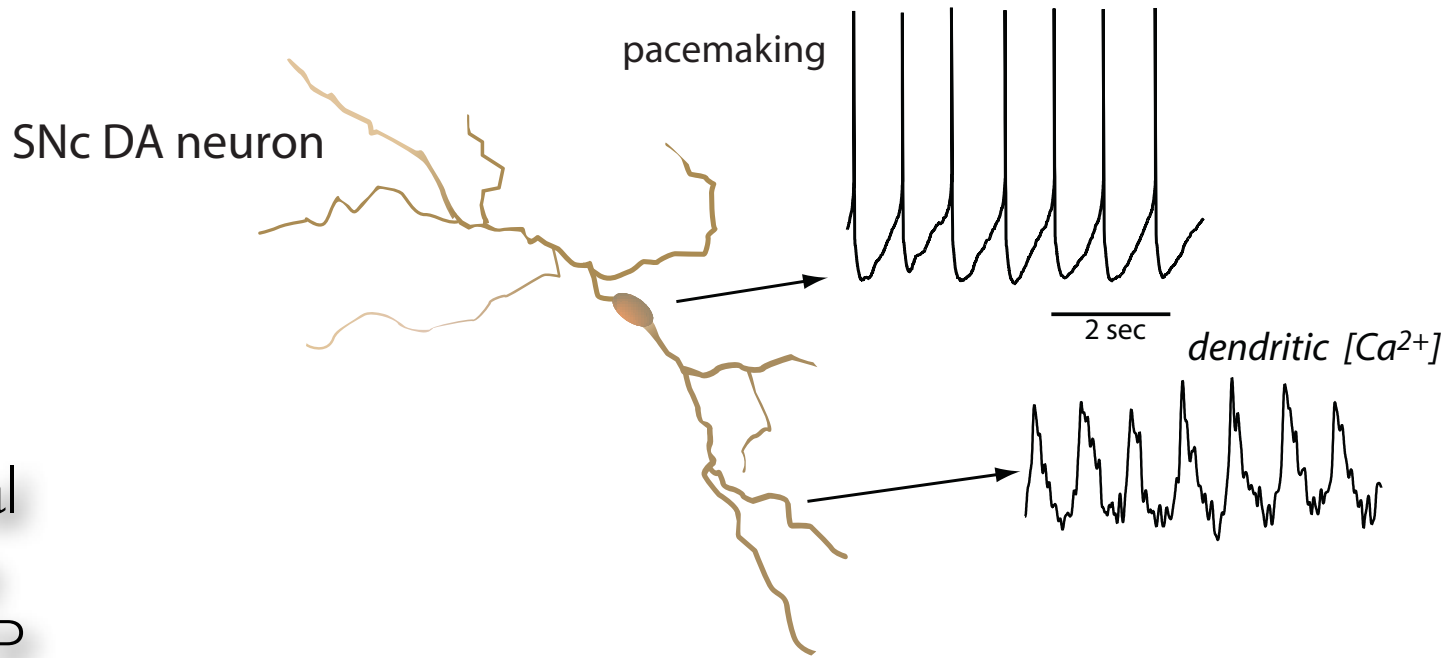
The calcium channel underlying these oscillations has a distinctive Cav1.3 pore.



Cav1.3 channels constitute 10% of all L-type channels in the brain and less that 3% of all voltage-dependent channels making it an attractive target..

The engagement of calcium channels could pose a metabolic load on SNc neuron...

Calcium is pumped up a steep electrochemical gradient at the expense of ATP



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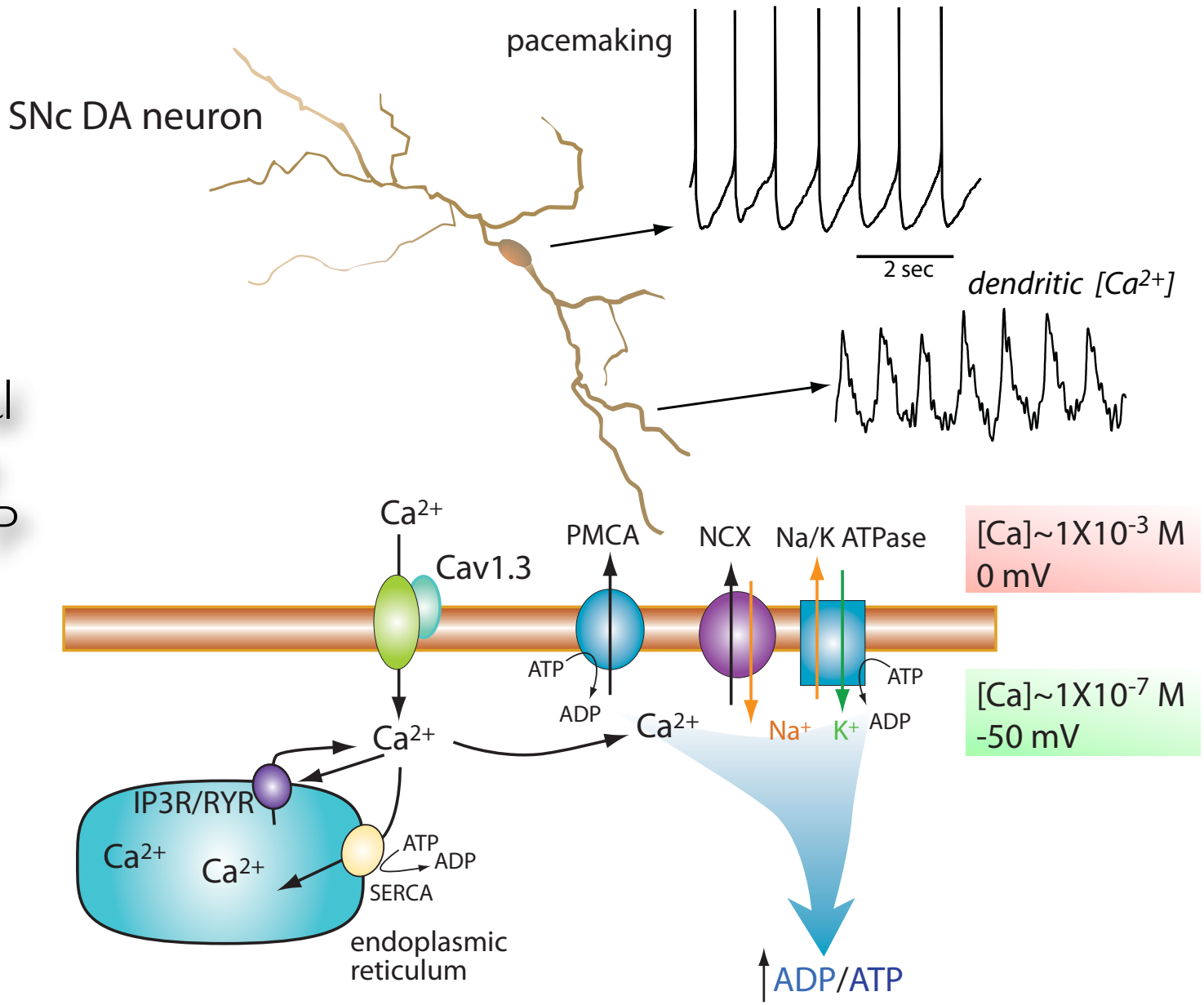

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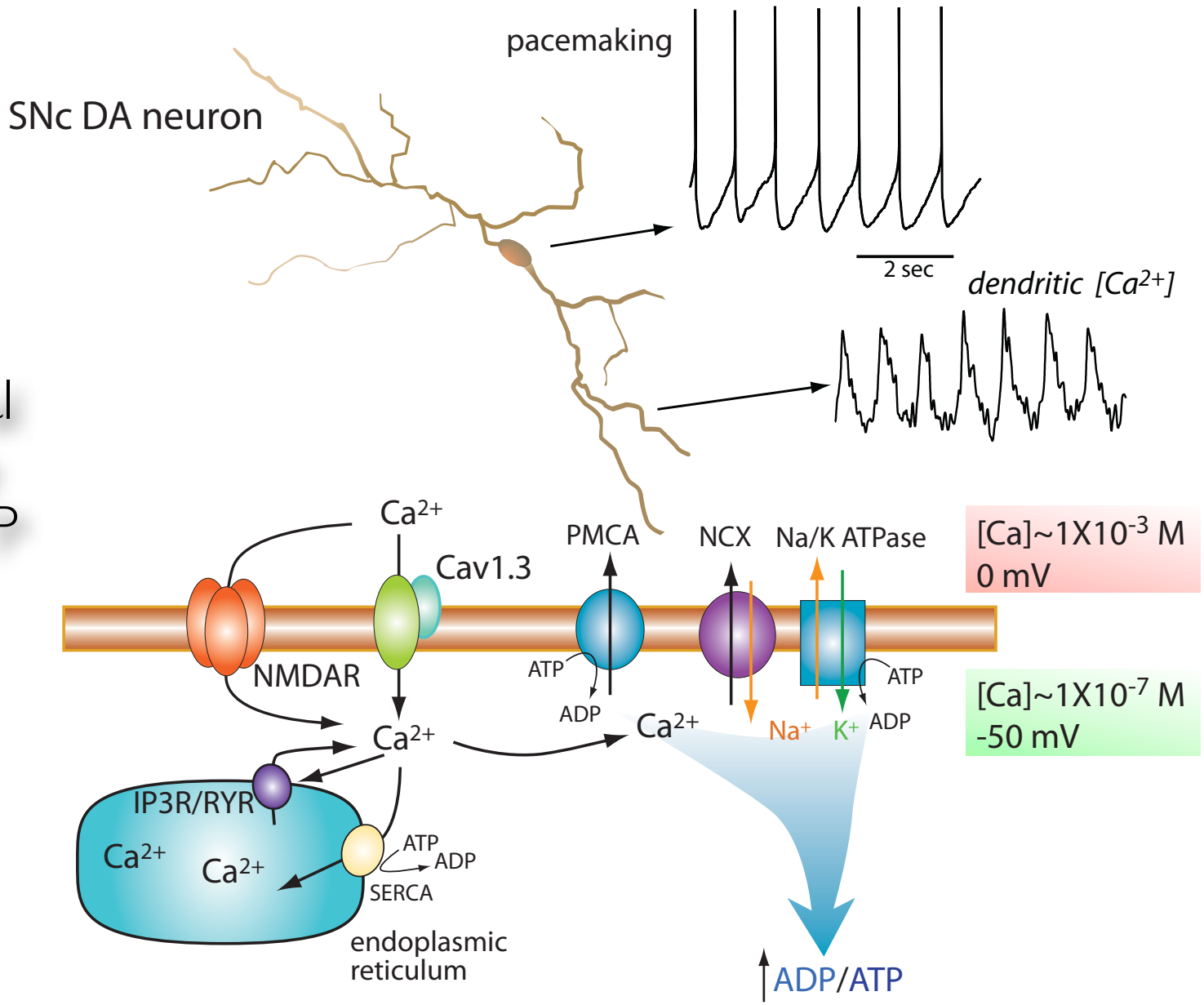

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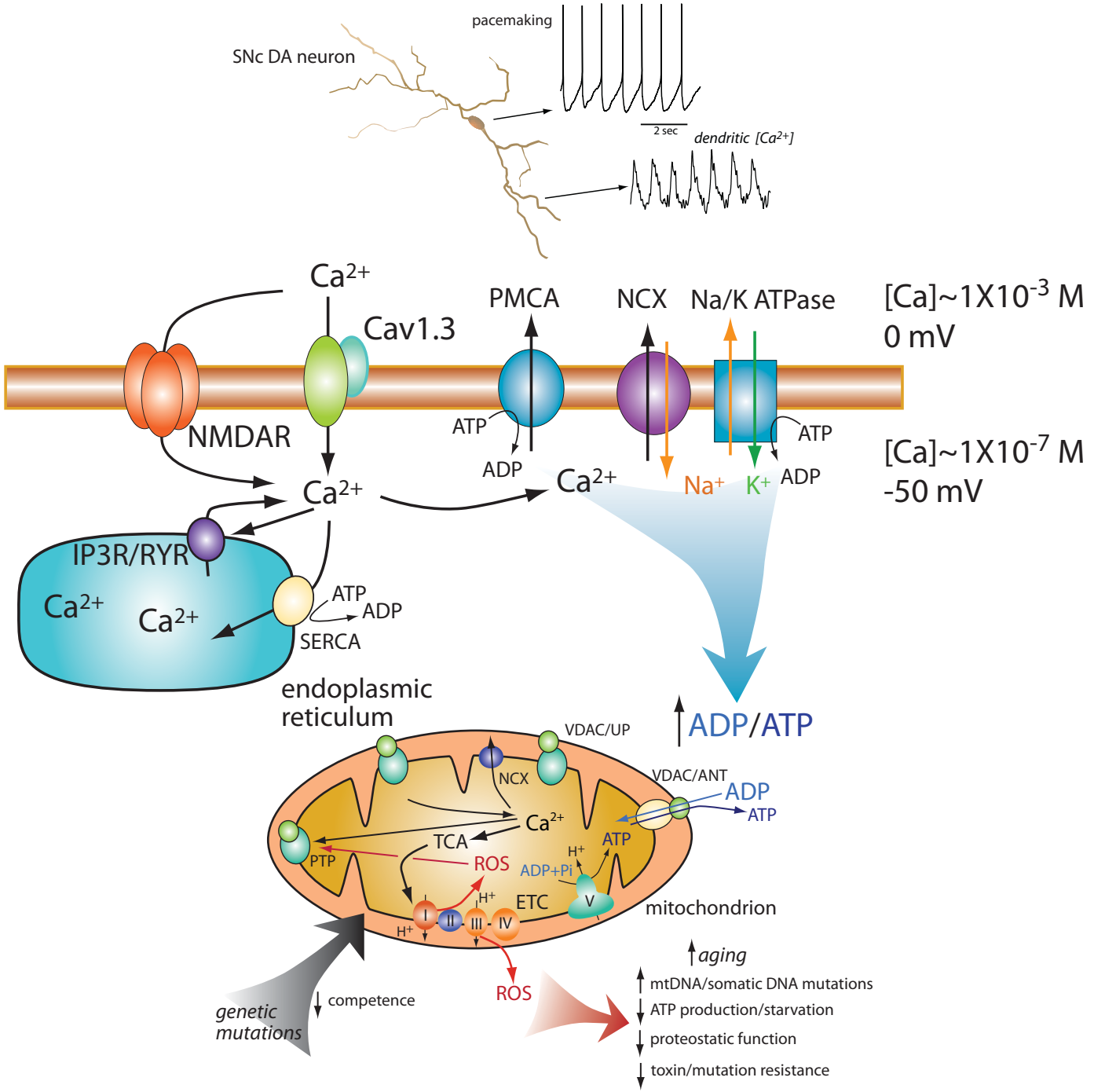


Calcium influx

The reliance upon calcium could pose a sustained metabolic burden

Calcium influx

ATP demand (energy)

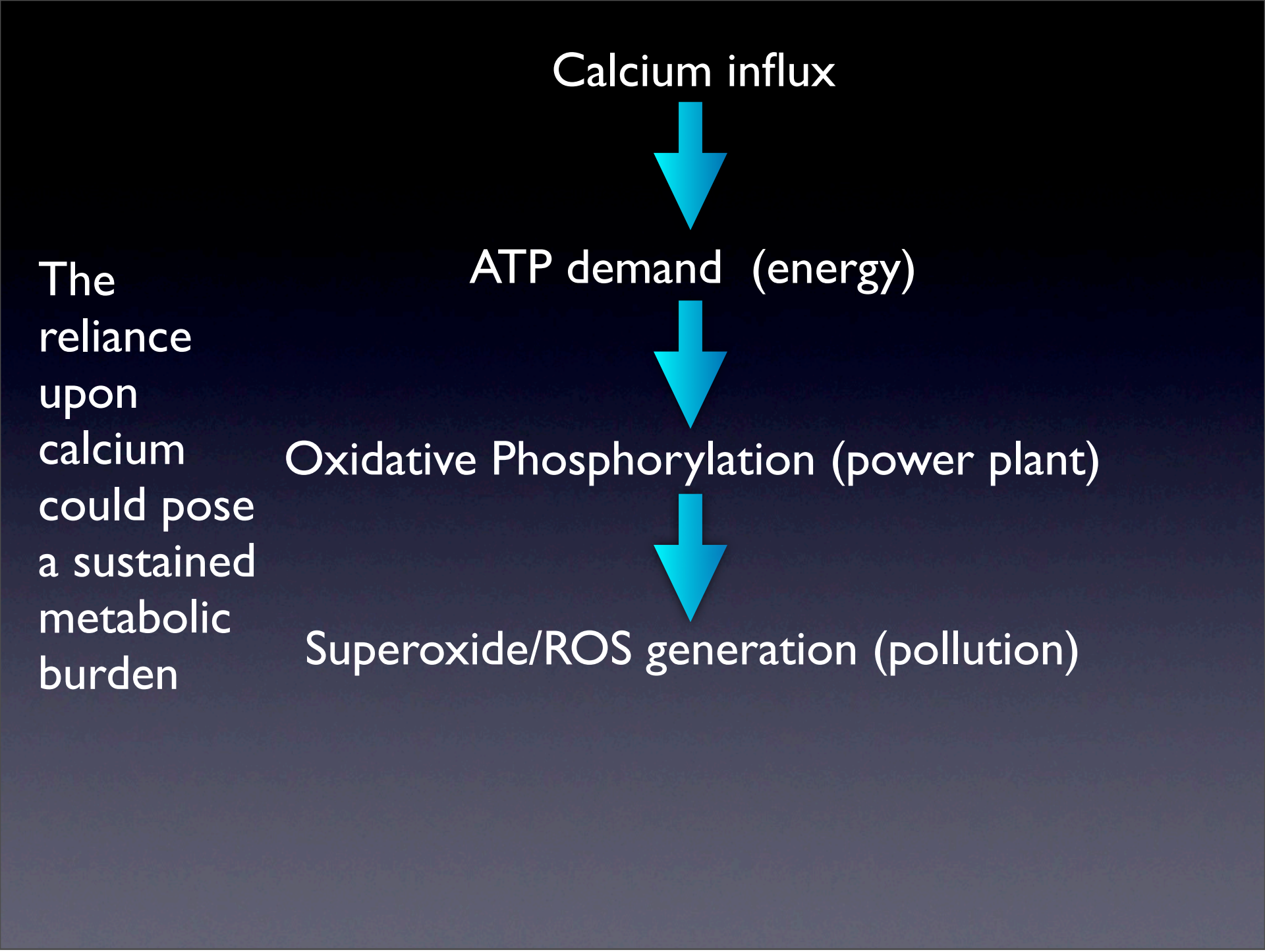
The reliance upon calcium could pose a sustained metabolic burden

Calcium influx

ATP demand (energy)

Oxidative Phosphorylation (power plant)

The reliance upon calcium could pose a sustained metabolic burden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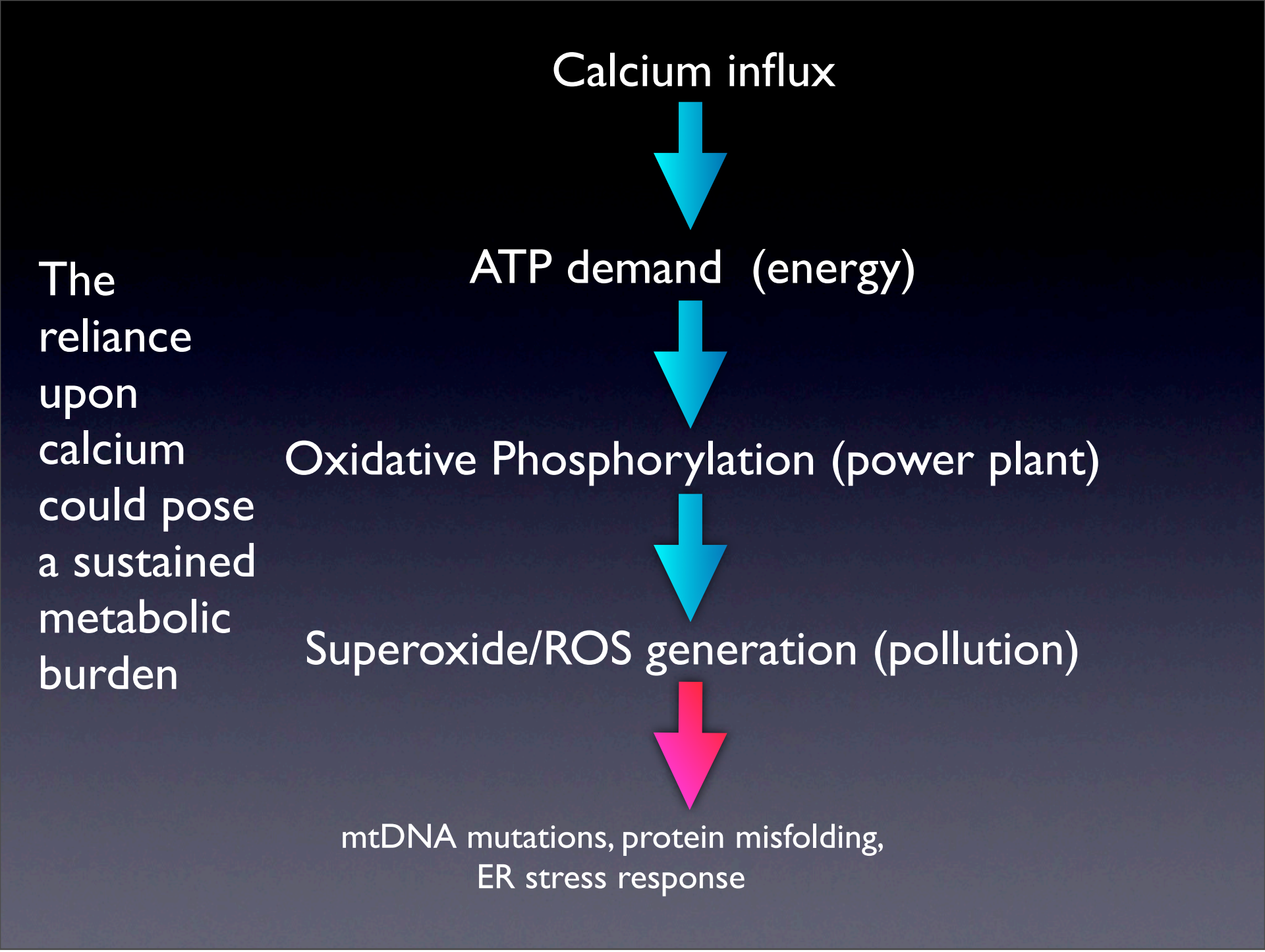
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mtDNA mutations, protein misfolding,
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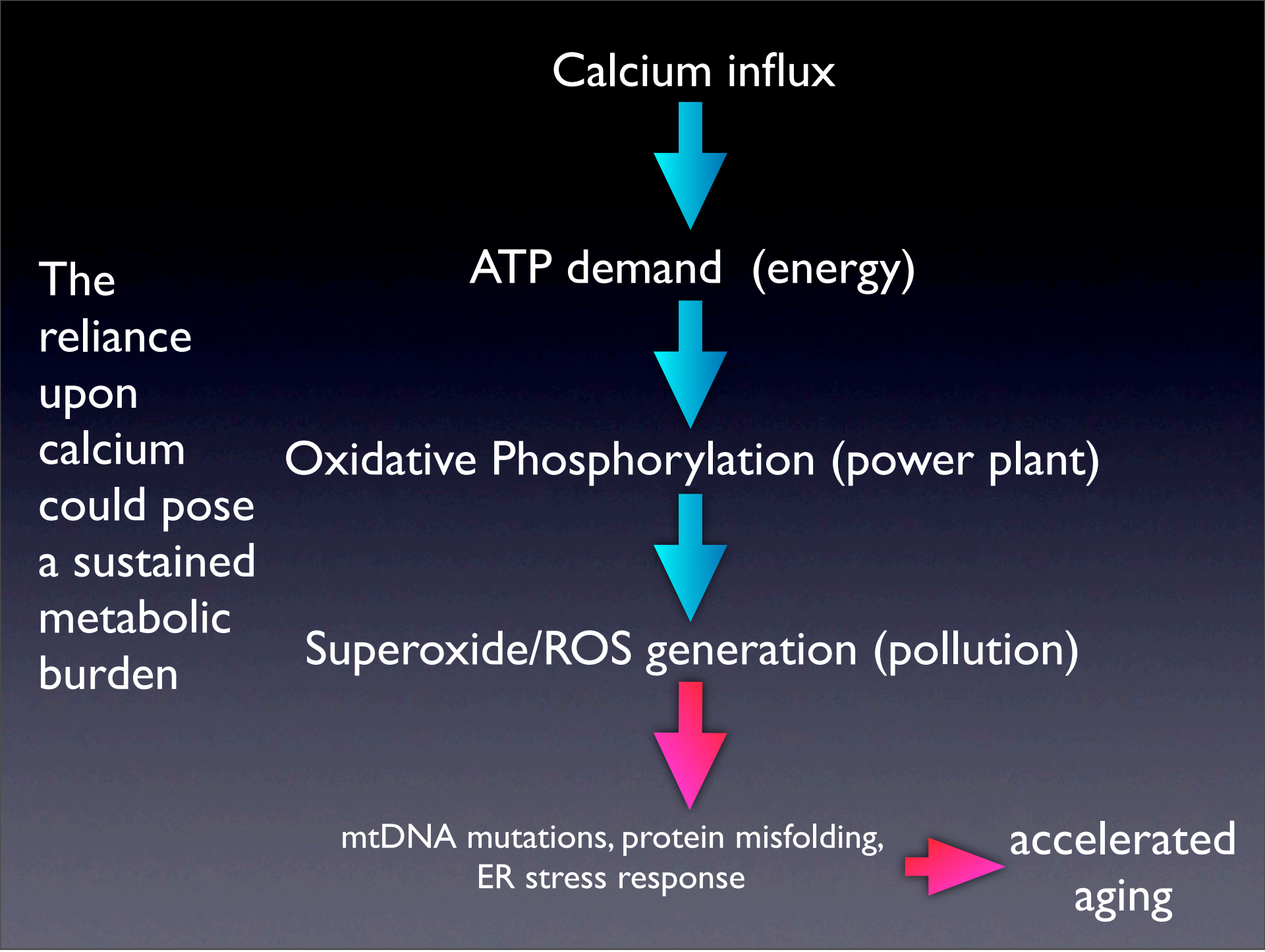
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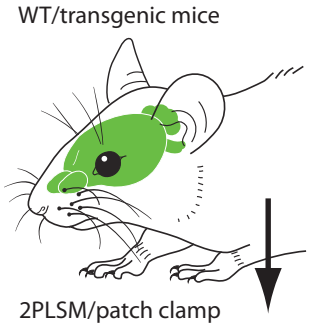
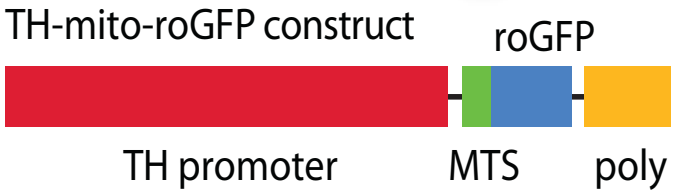
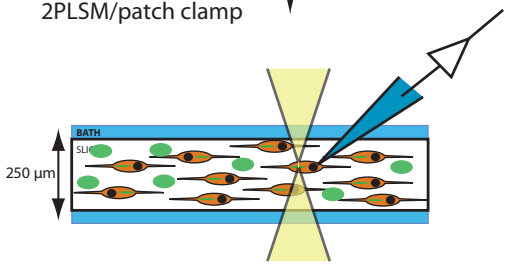
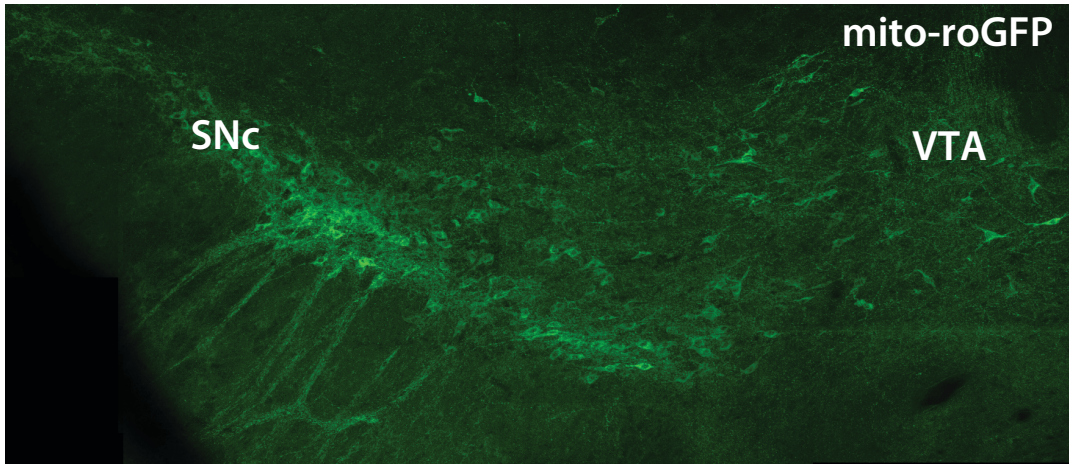
Nice theory but is it true?

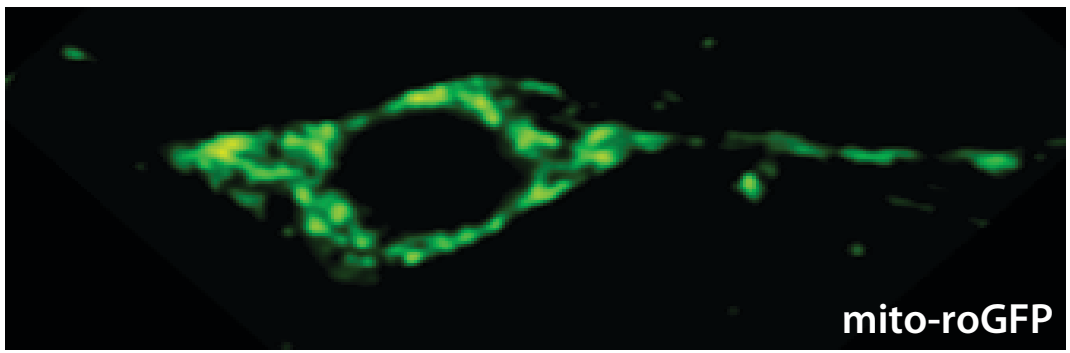
A transgenic mouse expressing mitochondrial roGFP in DA neurons was generated...

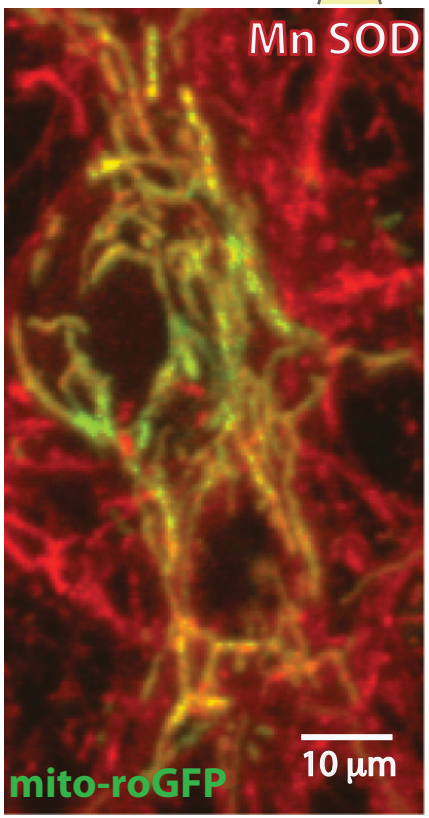


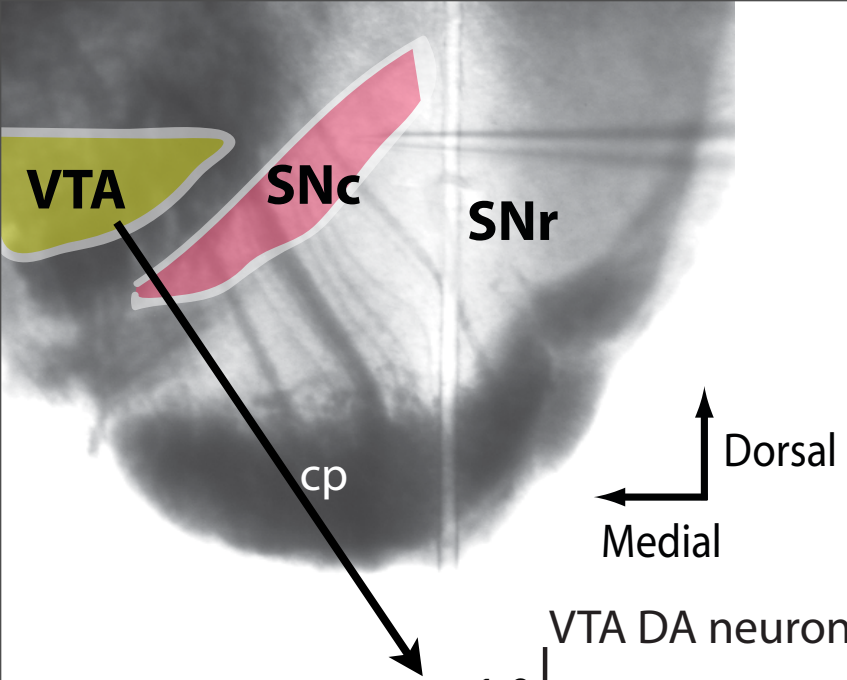


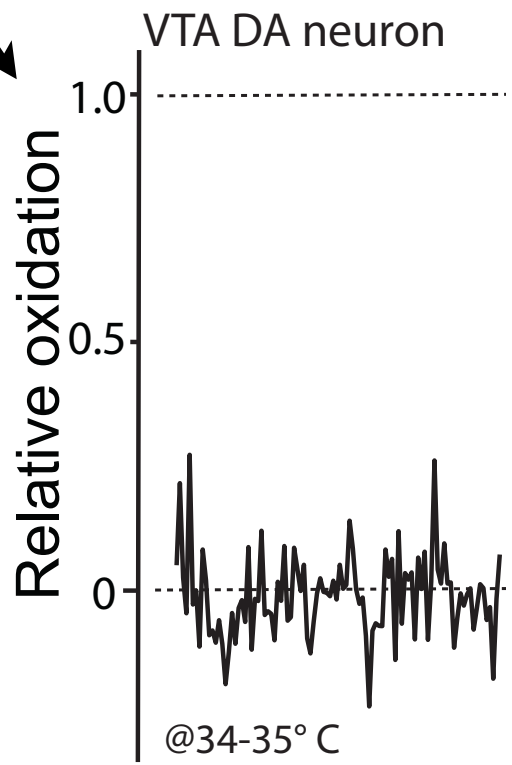




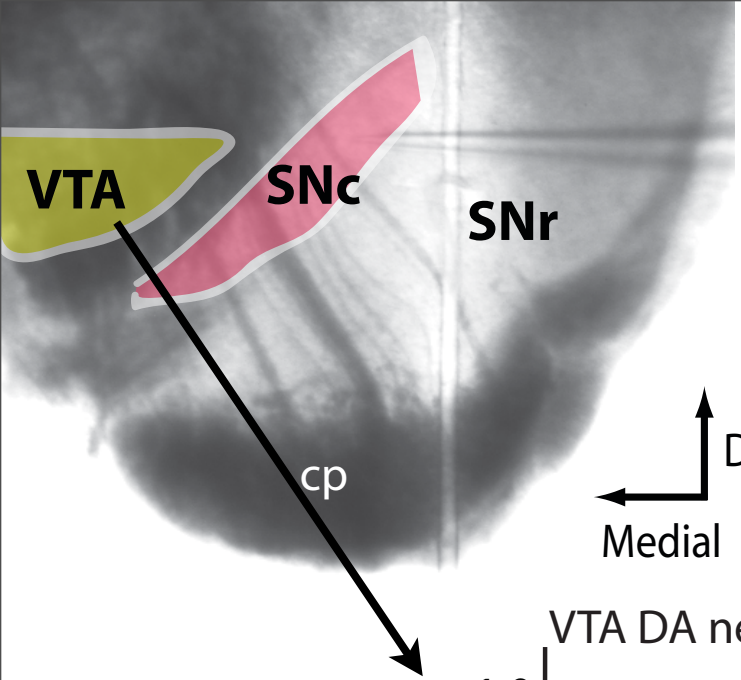




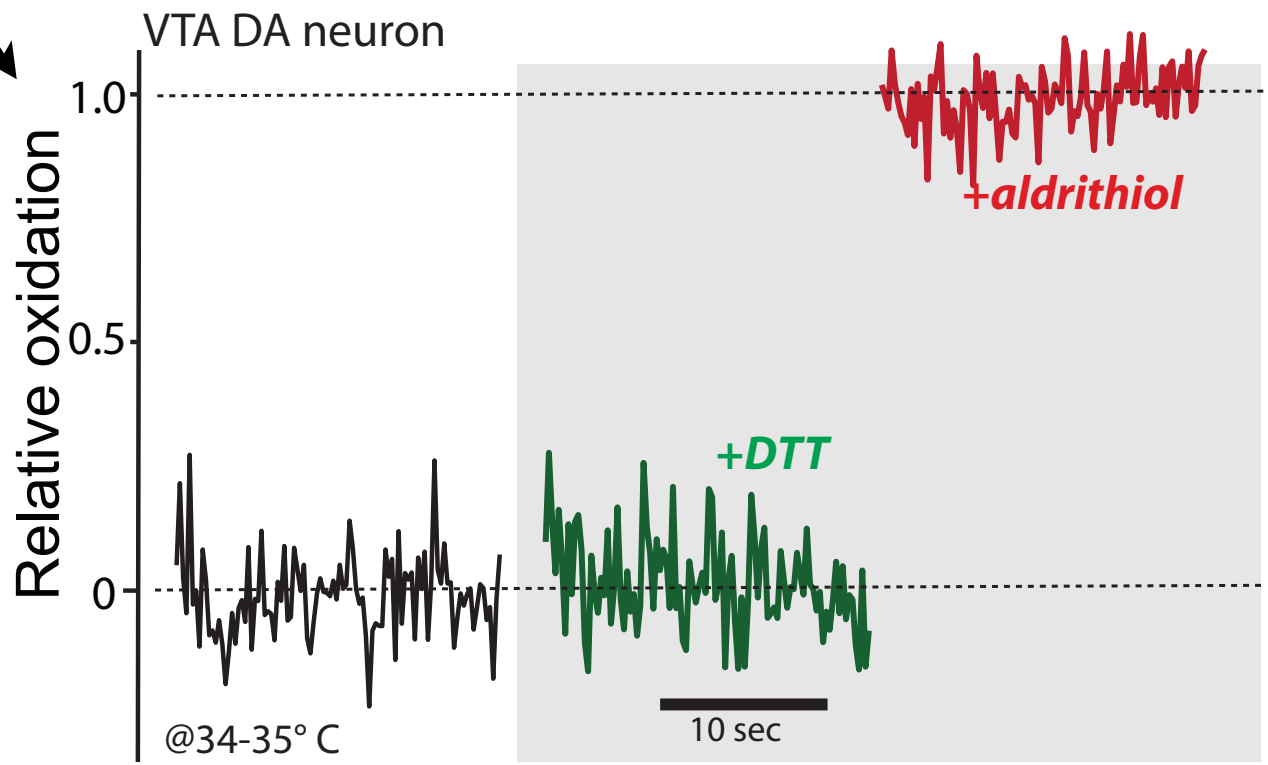


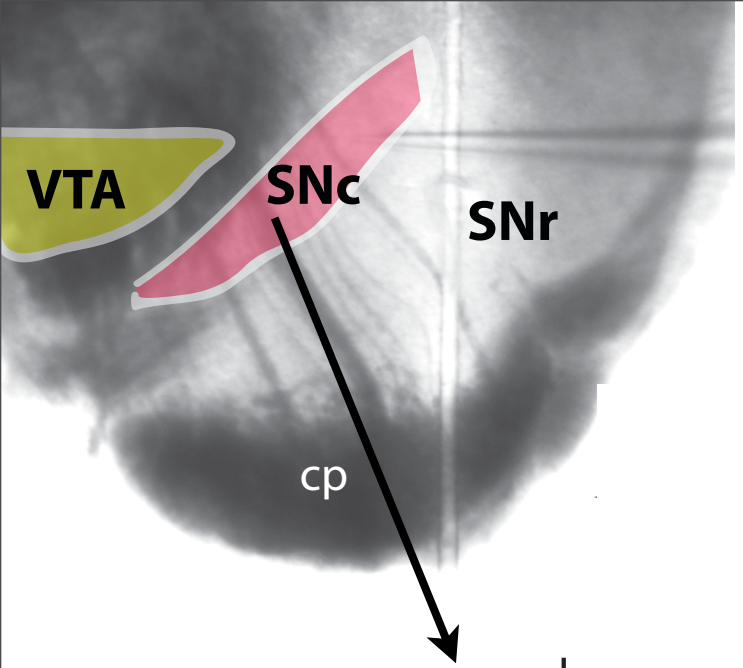


Are mitochondrial proteins oxidized in VTA neurons?

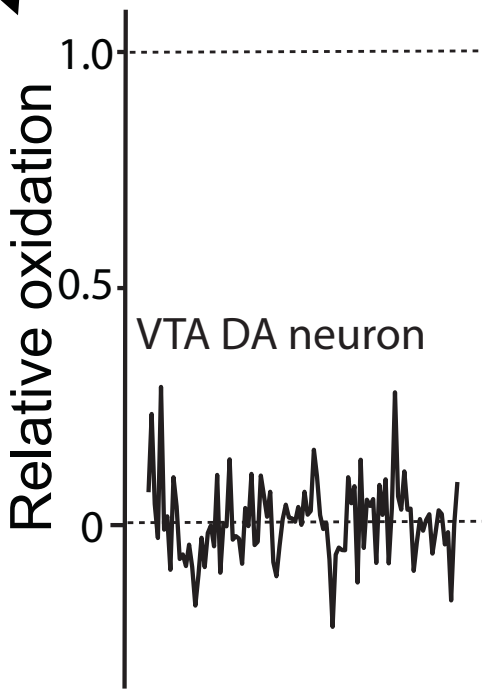


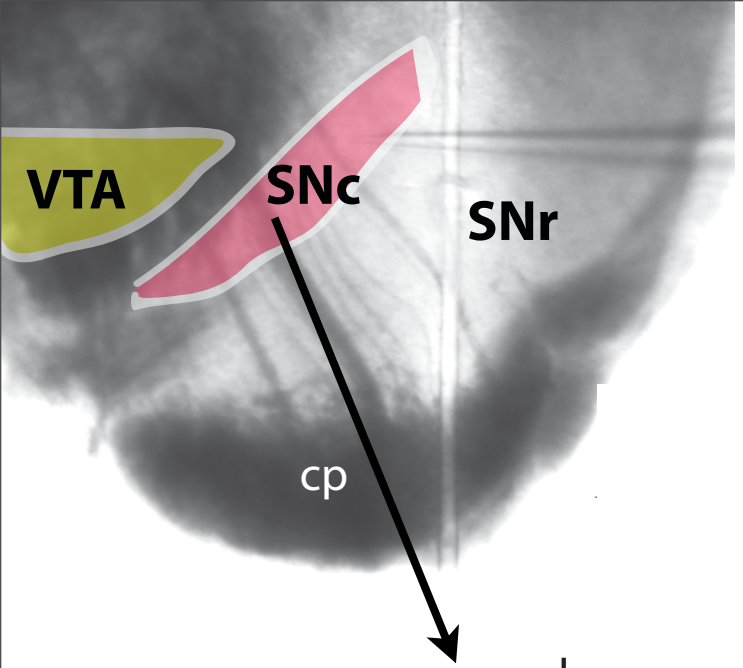
Are mitochondrial proteins oxidized in VTA neurons? No!





What about vulnerable SNc DA neurons?





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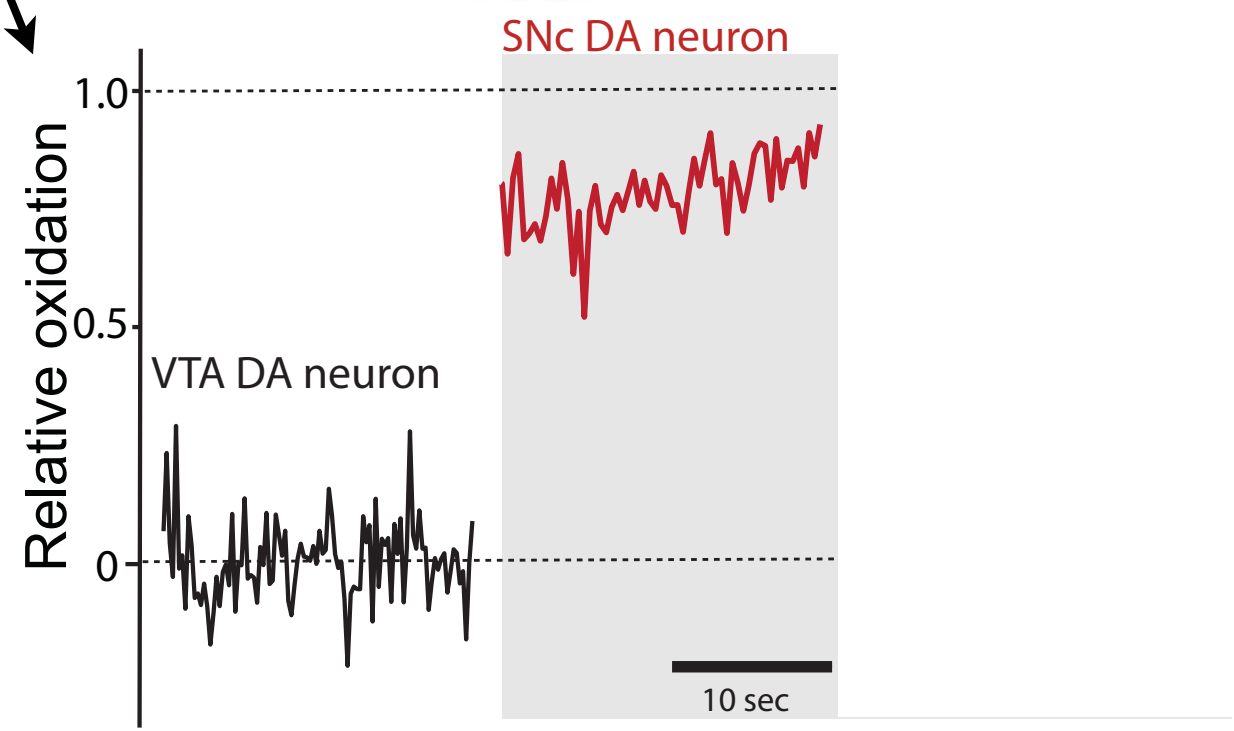

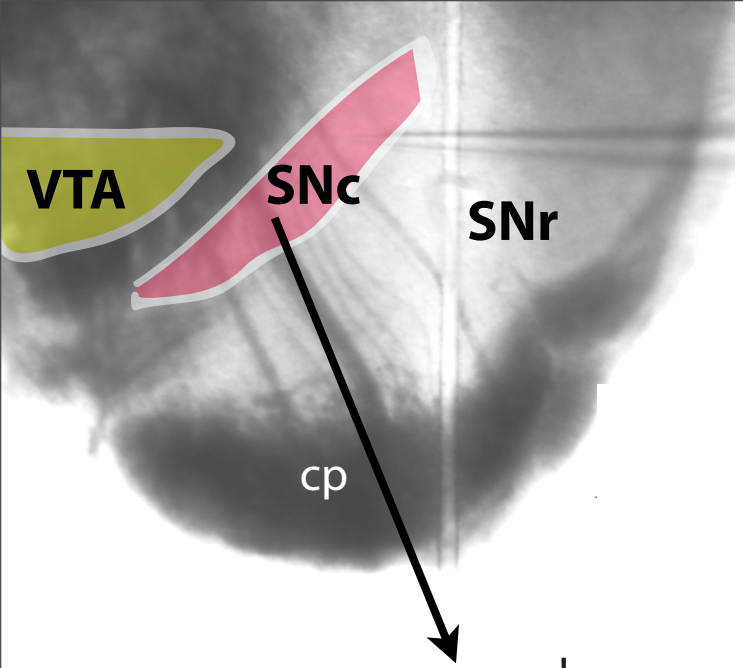

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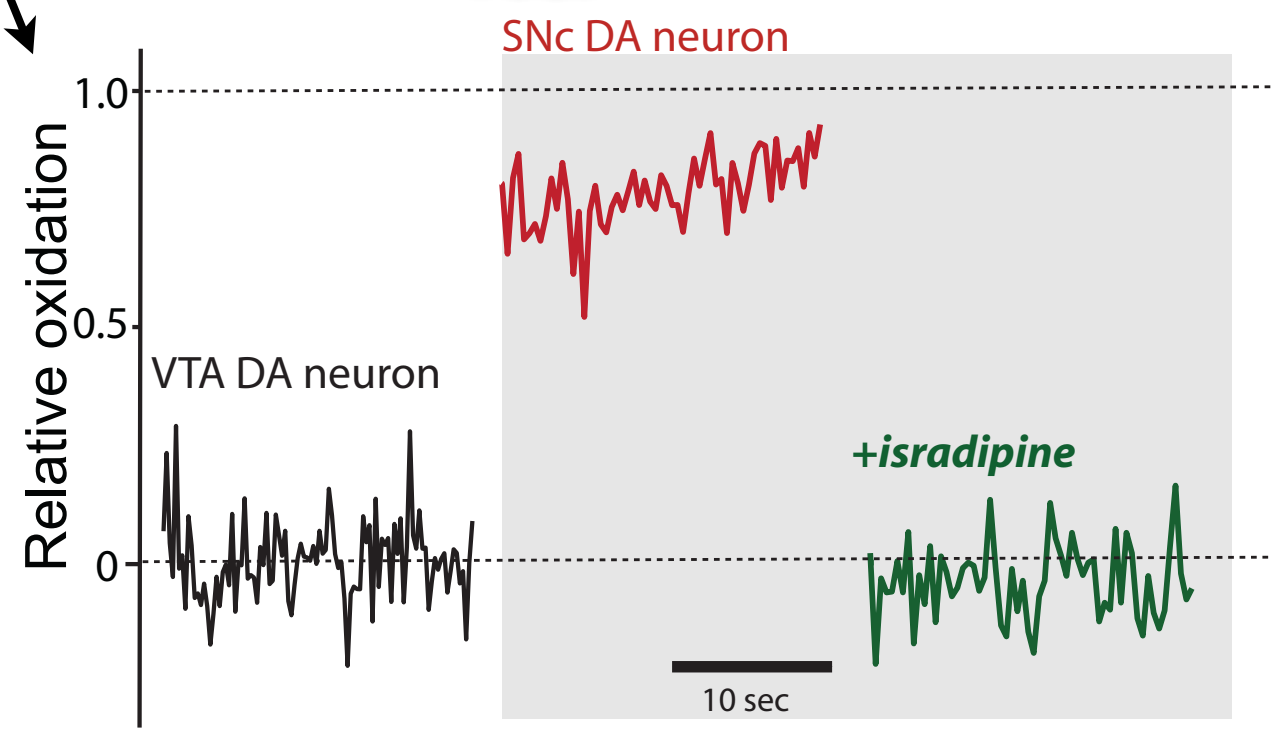
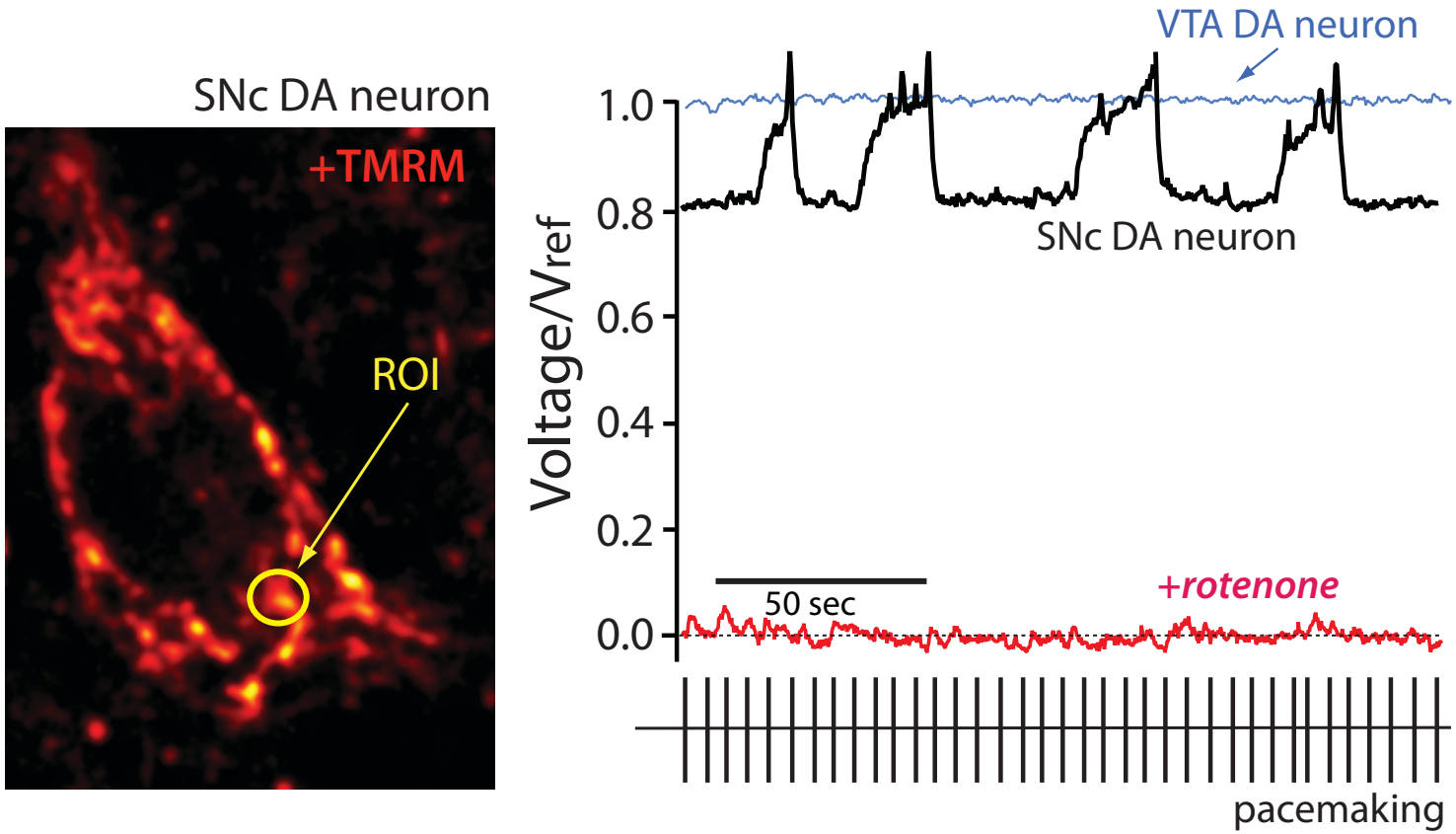
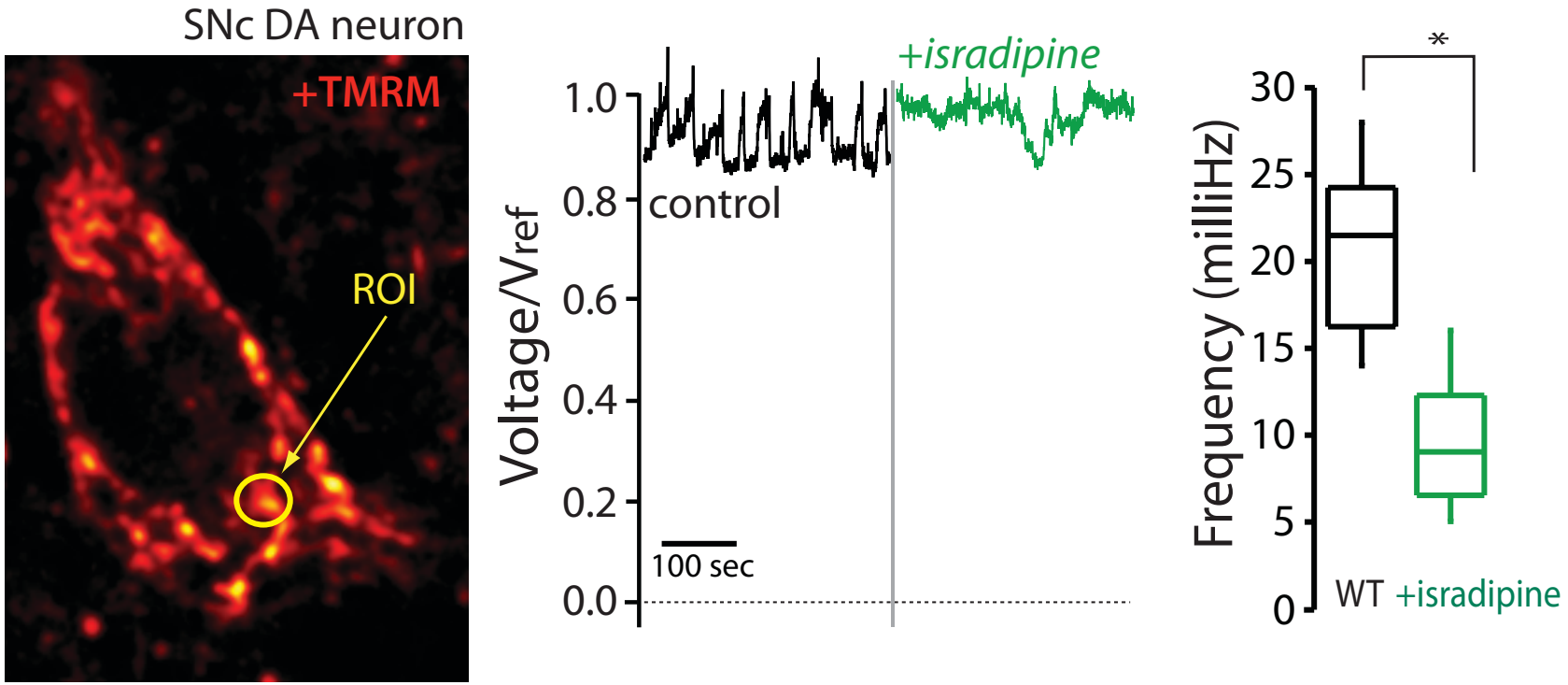


Oxidative stress in SNc DA neurons is accompanied by ‘flickering’ in mitochondrial potential, as measured by TMRM fluorescence...



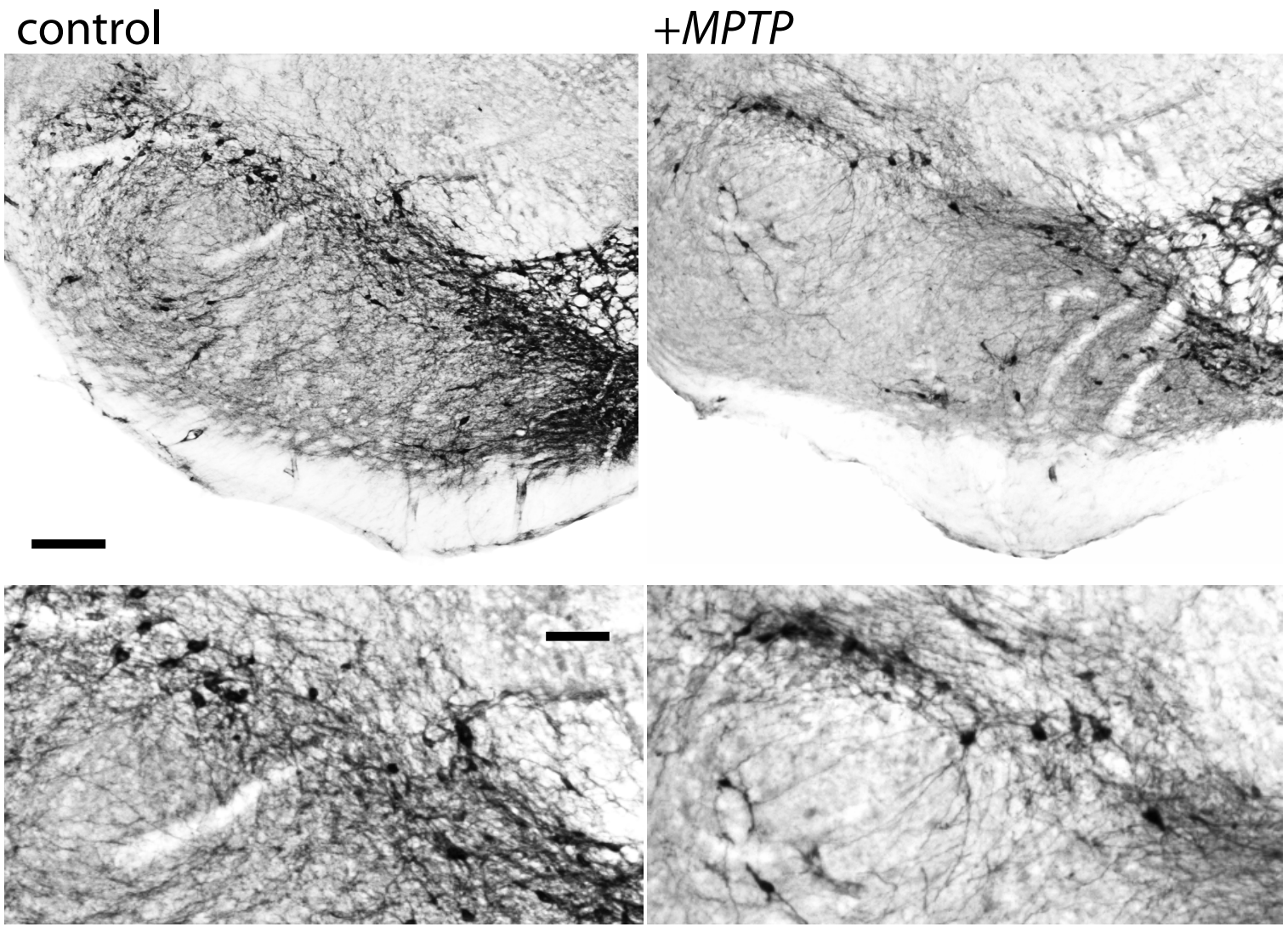
Oxidative stress in SNc DA neurons is accompanied by ‘flickering’ in mitochondrial potential, as measured by TMRM fluorescence...

...flickering is attenuated by isradipine antagonism of plasma membrane L-type channels...



Calcium entry increases the sensitivity of SNc DA neuron to toxins (MPTP, 6-OHDA, rotenone) used to create models of PD, as well as genetic mutations associated with the disease.

Chronic MPTP treatment leads to a loss of SNc neurons...



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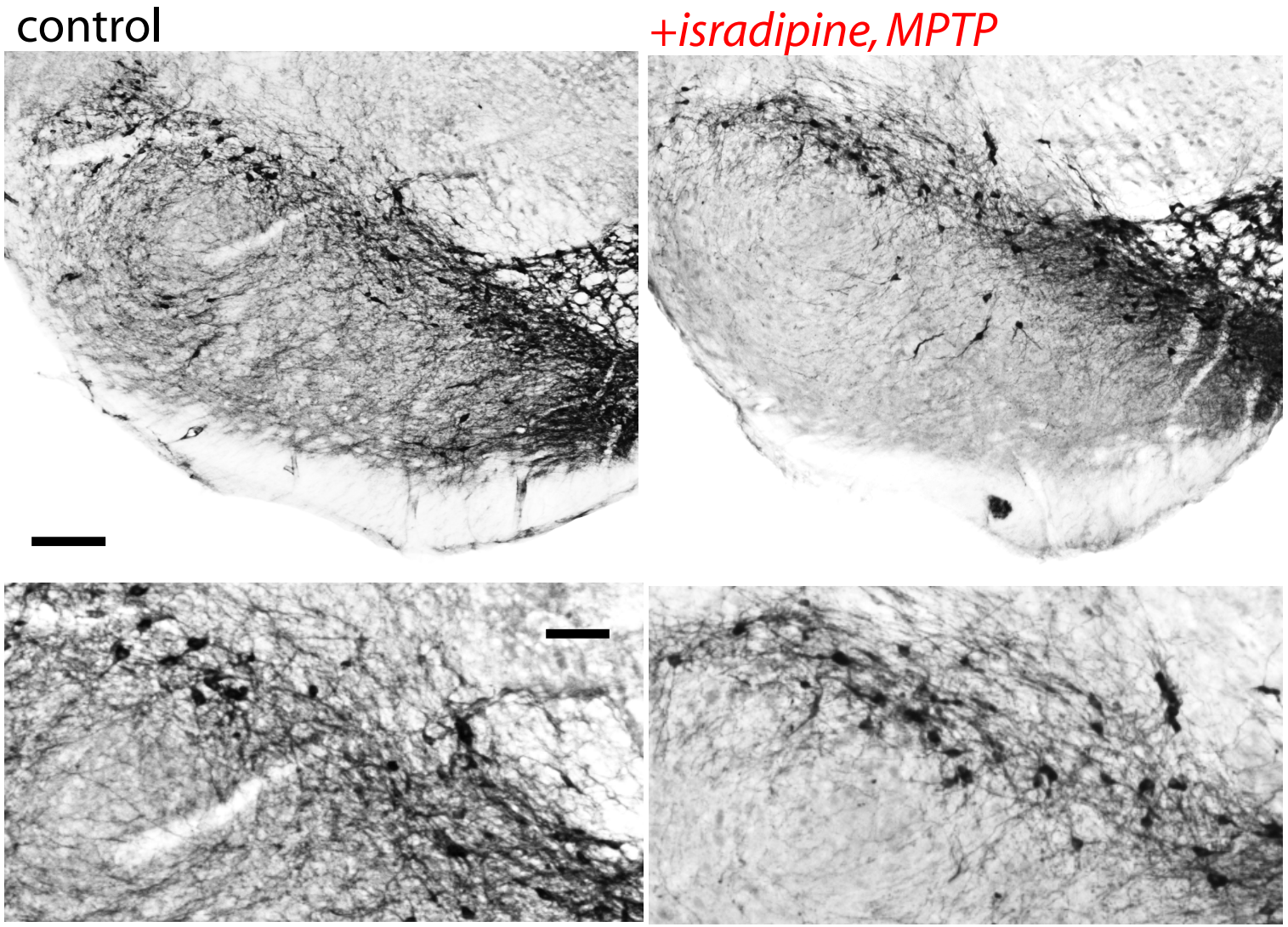

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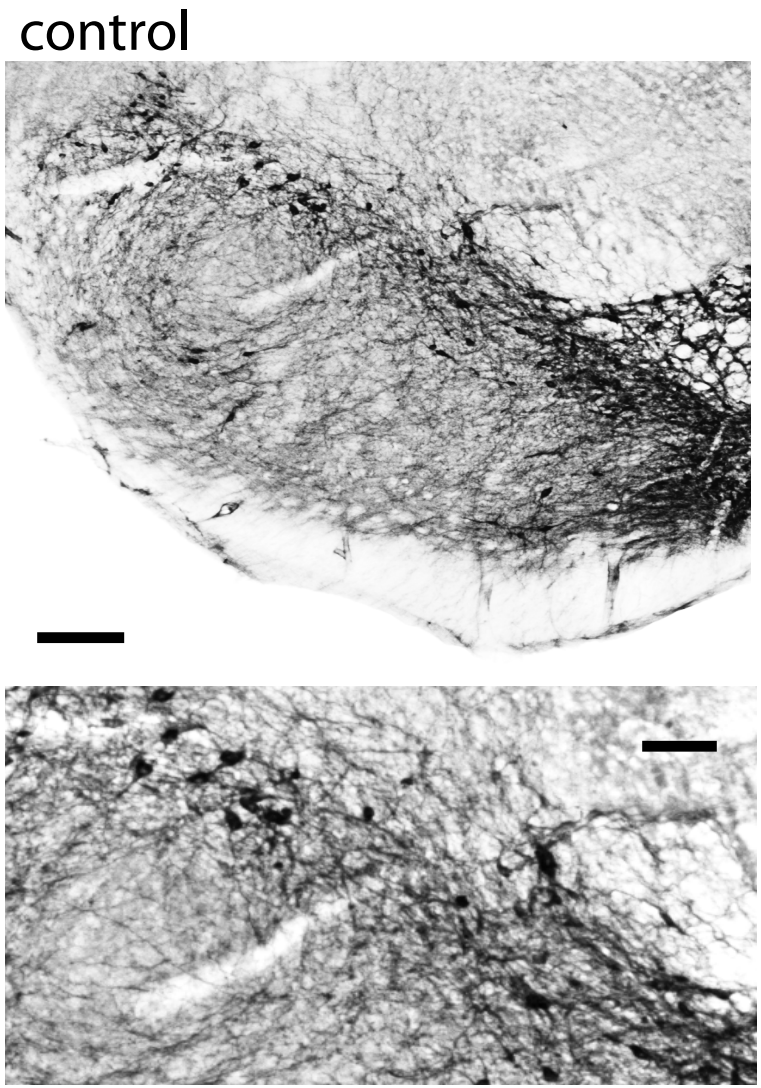

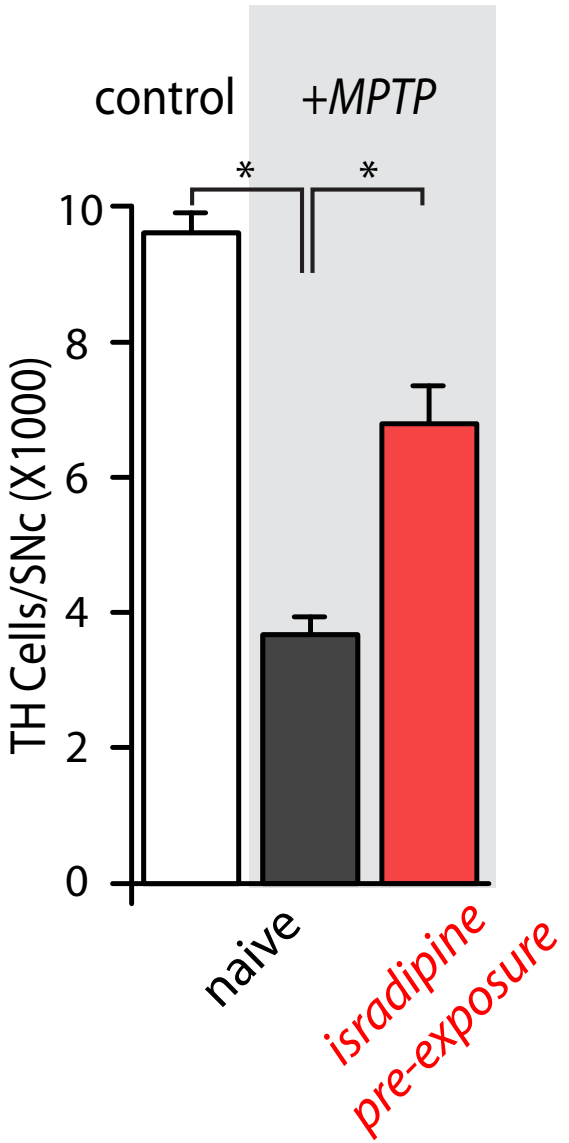

Does this have anything to do with PD?

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Cav1 antagonists have been used for decades to treat hypertension...

Epidemiological analysis has confirmed a diminished risk of PD in patients treated with brain penetrant dihydropyridines...

Neurology, Feb. 6, 2008

Published Ahead of Print on February 6, 2008 as 10.1212/01.wnl.0000303818.38960.44

Use of antihypertensives and the risk of Parkinson disease

Claudia Becker, PhD
Susan S. Jick, DSc
Christoph R. Meier, PhD

Address correspondence and reprint requests to Dr. Christoph R. Meier, Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland
Meierch@uhbs.ch

ABSTRACT

Background: Recent studies related angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers to possible neuroprotective effects. Little is known about neuroprotection of angiotensin II (AT II) antagonists or beta-blockers.

Objective: To explore the association between antihypertensive drug use and the risk of developing a first-time diagnosis of Parkinson disease (PD).

Methods: This was a case-control analysis within the UK-based General Practice Research Database. Cases were ≥40 years of age with an incident PD diagnosis between 1994 and 2005. We matched one control to each PD case on age, sex, general practice, index date, and duration of previous history in the database. We assessed antihypertensive drug use by timing and by exposure duration. We calculated ORs using conditional logistic regression, adjusted for body mass index, smoking, and various cardiovascular, metabolic, and psychiatric diseases and dementia.

Results: We identified 3,637 cases with a first-time diagnosis ofi diopathic PD and an equal number of matched controls. As compared to nonuse of antihypertensive drugs, the adjusted OR for current use of ≥30 prescriptions was 1.08 (95% CI 0.85 to 1.37) for ACE inhibitors, 0.91 (95% CI 0.41 to 2.00) for AT II antagonists, 1.16 (95% CI 0.95 to 1.41) for beta-blockers, and 0.77 (95% CI 0.63 to 0.95) for calcium channel blockers.

Epidemiological analysis has confirmed a diminished risk of PD in patients treated with brain penetrant dihydropyridines...

L-Type Calcium Channel Blockers and Parkinson Disease in Denmark

Beate Ritz, MD, PhD, [1] Shannon L. Rhodes, PhD, [1] Lei Qian, PhD, [2] Eva Schernhammer, MD, DrPH, [3] Jørgen H. Olsen, DMSc, [4] and Søren Friis, MD [4]

Objective: This study was undertaken to investigate L-type calcium channel blockers of the dihydropyridine class for association with Parkinson disease (PD), because some of these drugs traverse the blood–brain barrier, are potentially neuroprotective, and have previously been evaluated for impact on PD risk.
Methods: We identified 1,931 patients with a first-time diagnosis for PD between 2001 and 2006 as reported in the Danish national hospital/outpatient database and density matched them by birth year and sex to 9,651 controls from the population register. The index date for cases and their corresponding controls was advanced to the date of first recorded prescription for anti-Parkinson drugs, if prior to first PD diagnosis in the hospital records. Prescriptions were determined from the national pharmacy database. In our primary analyses, we excluded all calcium channel blocker prescriptions 2 years before index date/PD diagnosis.
Results: Employing logistic regression analysis adjusting for age, sex, diagnosis of chronic pulmonary obstructive disorder, and Charlson comorbidity score, we found that subjects prescribed dihydropyridines (excludes amlodipine) between 1995 and 2 years prior to the index date were less likely to develop PD (odds ratio, 0.73; 95% confidence interval, 0.54–0.97); this 27% risk reduction did not differ with length or intensity of use. Risk estimates were close to null for the peripherally acting drug amlodipine and for other antihypertensive medications.
Interpretation: Our data suggest a potential neuroprotective role for centrally acting L-type calcium channel blockers of the dihydropyridine class in PD that should be further investigated in studies that can distinguish between types of L-type channel blockers.

ANN NEUROL 2010;67:600–606

Epidemiological analysis has confirmed a diminished risk of PD in patients treated with brain penetrant dihydropyridines...

TABLE 2: Associations between L-Type Dihydropyridine CCB Prescriptions (2-Year Lag) and Parkinson Disease (N =11,582)

Ever Use	Cases, n=1,931, No. (%)	Controls, n=9,651, No. (%)	Model 1, OR (95% CI) [a]	Model 2, OR (95% CI) [b]	Model 3, OR (95% CI) [c]
Dihydropyridine CCBs[d]					
No	1,876 (97.2)	9,283 (96.2)	Reference	Reference	Reference
Yes	55 (2.8)	368 (3.8)	0.74 (0.55–0.99)	0.73 (0.54–0.97)	0.70 (0.52–0.94)
Amlodipine					
No	1,770 (91.7)	8,885 (92.1)		Reference	
Yes	161 (8.3)	766 (7.9)		1.04 (0.87–1.25)	

[a]Adjusted for age and sex. [b]Adjusted for age, sex, COPD (5-year lag), and Charlson index (5-year lag). [c]Adjusted for age, sex, COPD (5-year lag), Charlson index (5-year lag), and other antihypertensive drugs (nondihydropyridine CCBs, amlodipine, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists, 5-year lag). [d]Excludes amlodipine. CCB = calcium channel blocker; OR = odds ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease.

Our results suggest that neuron loss in PD is primarily attributable to 'wear and tear' or accelerated aging...

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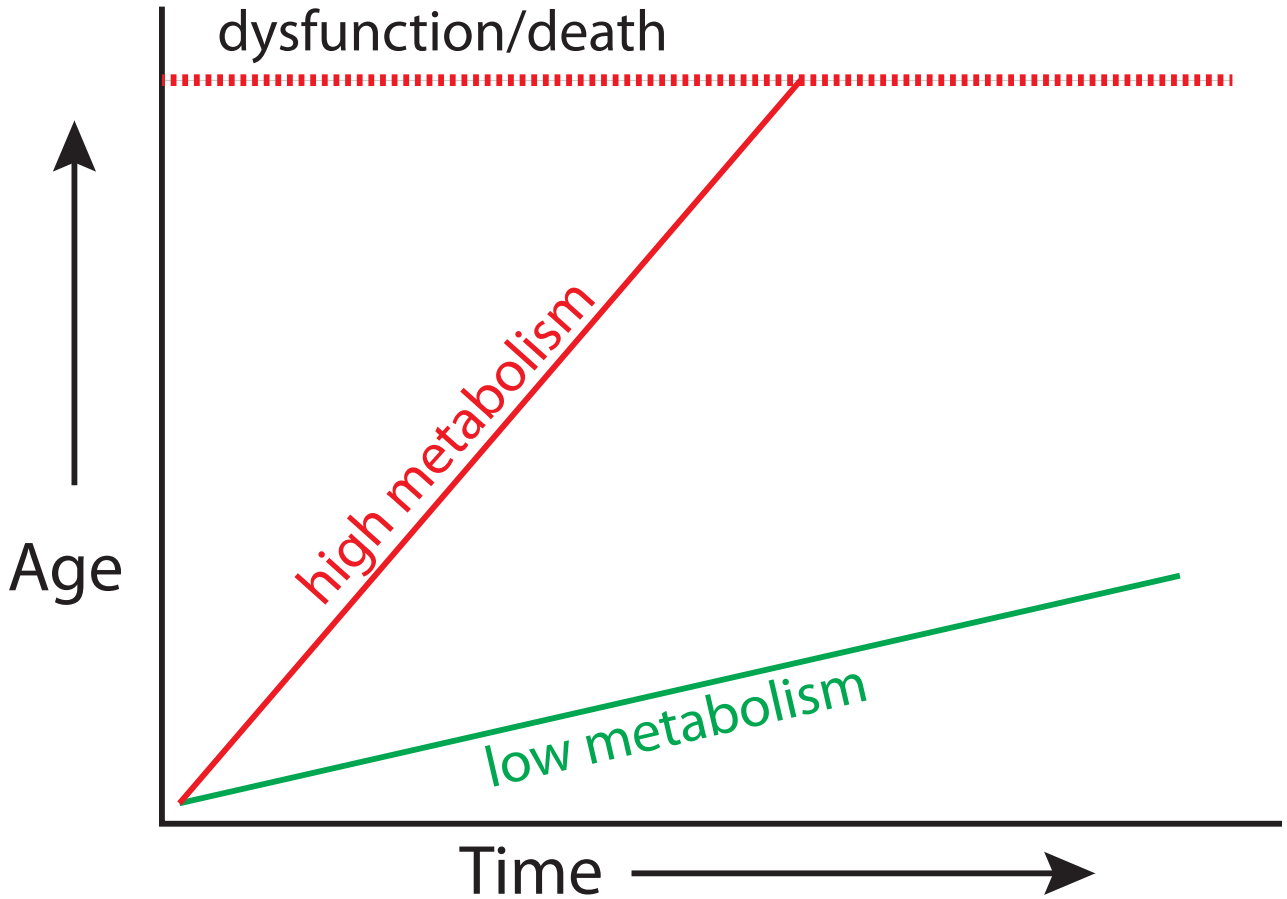
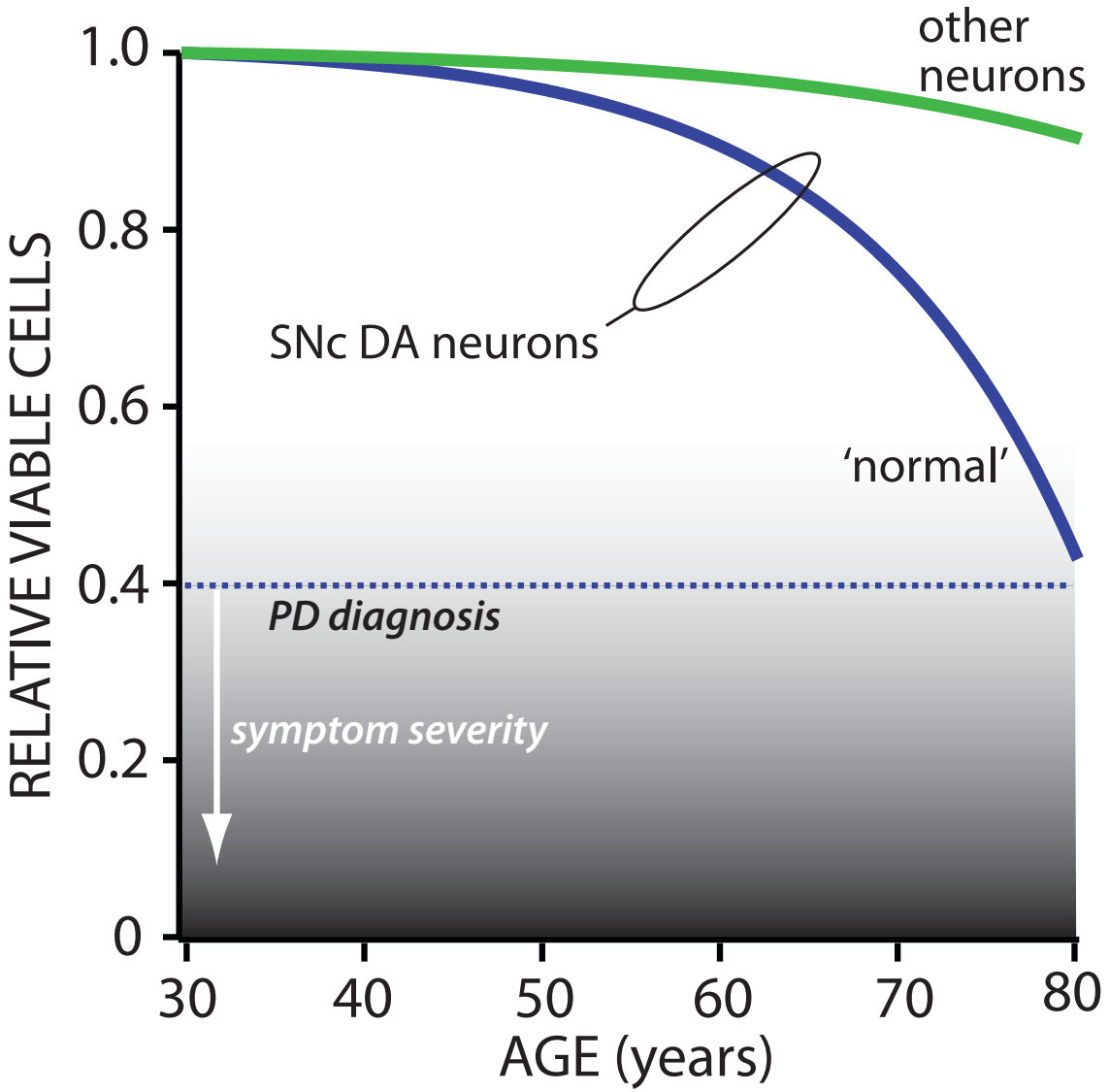
That is, SNc DA neurons were not designed to last...

As with organisms, a high rate of metabolism (and free radical production) might cause SNc DA neurons to age more rapidly...



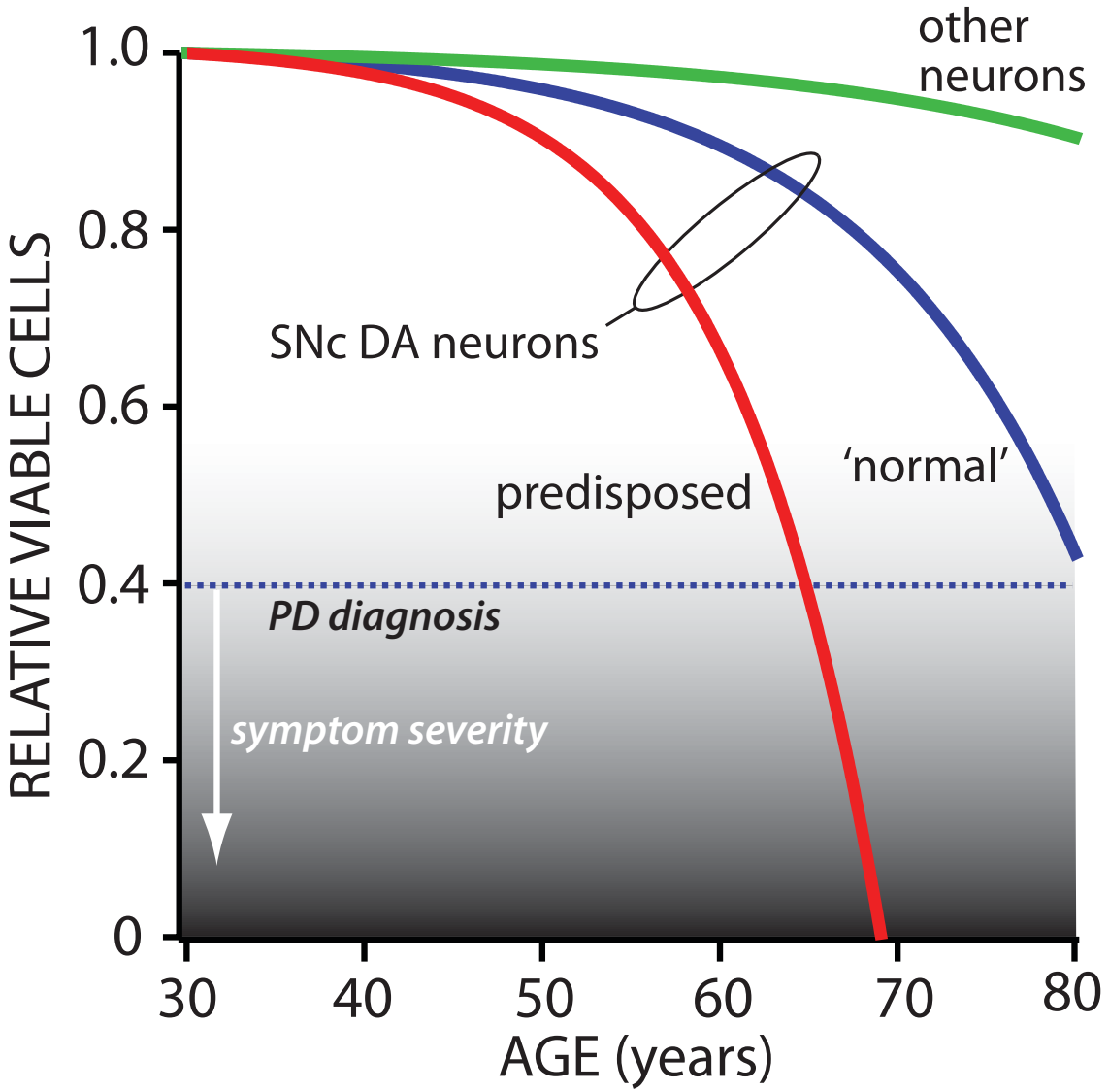
The loss of SNc DA neurons must begin well before the onset of symptoms...

'Normal' DA neurons are at risk because of their high basal stress level.
As defects accumulate, cell loss and phenotypic decline should accelerate.



The loss of SNc DA neurons must begin well before the onset of symptoms...

The rate of cell loss over decades could be accelerated by genetic predisposition or environmental risk factors



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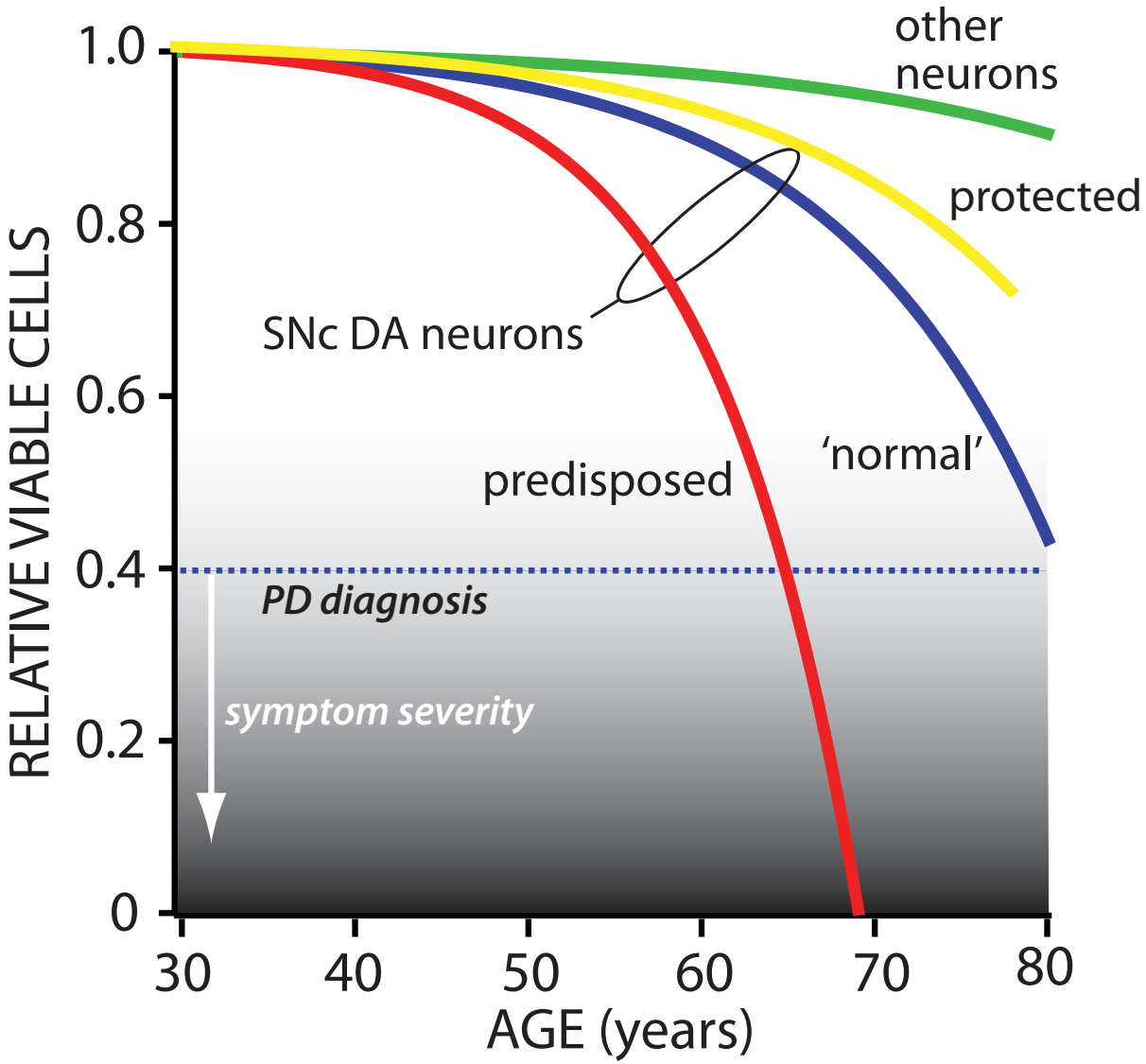
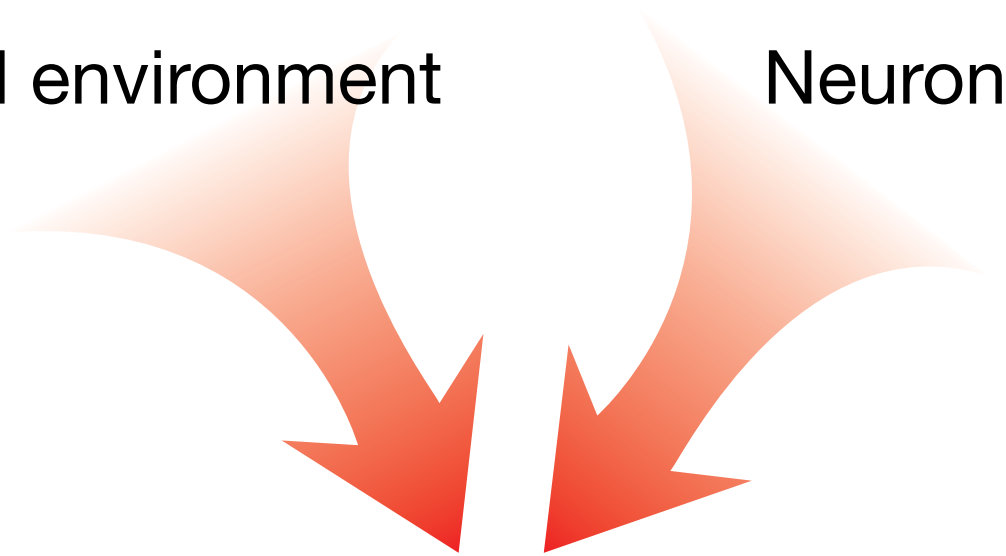


By pharmacologically ‘re-designing’ vulnerable neurons, we should be able to halt pathogenesis...

Genes and environment

Neuronal design



Pathogenesis

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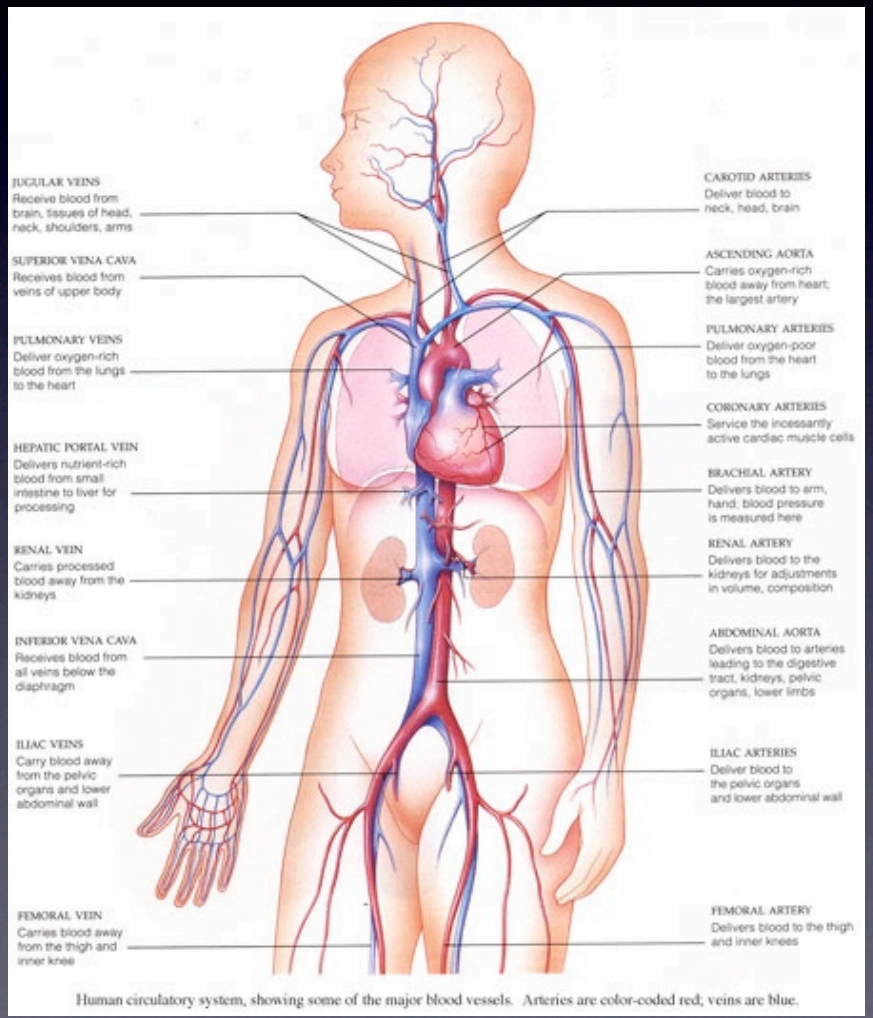
Genes and environment

A multi-center neuroprotection trial proposal using isradipine (DynaCirc) is underway.

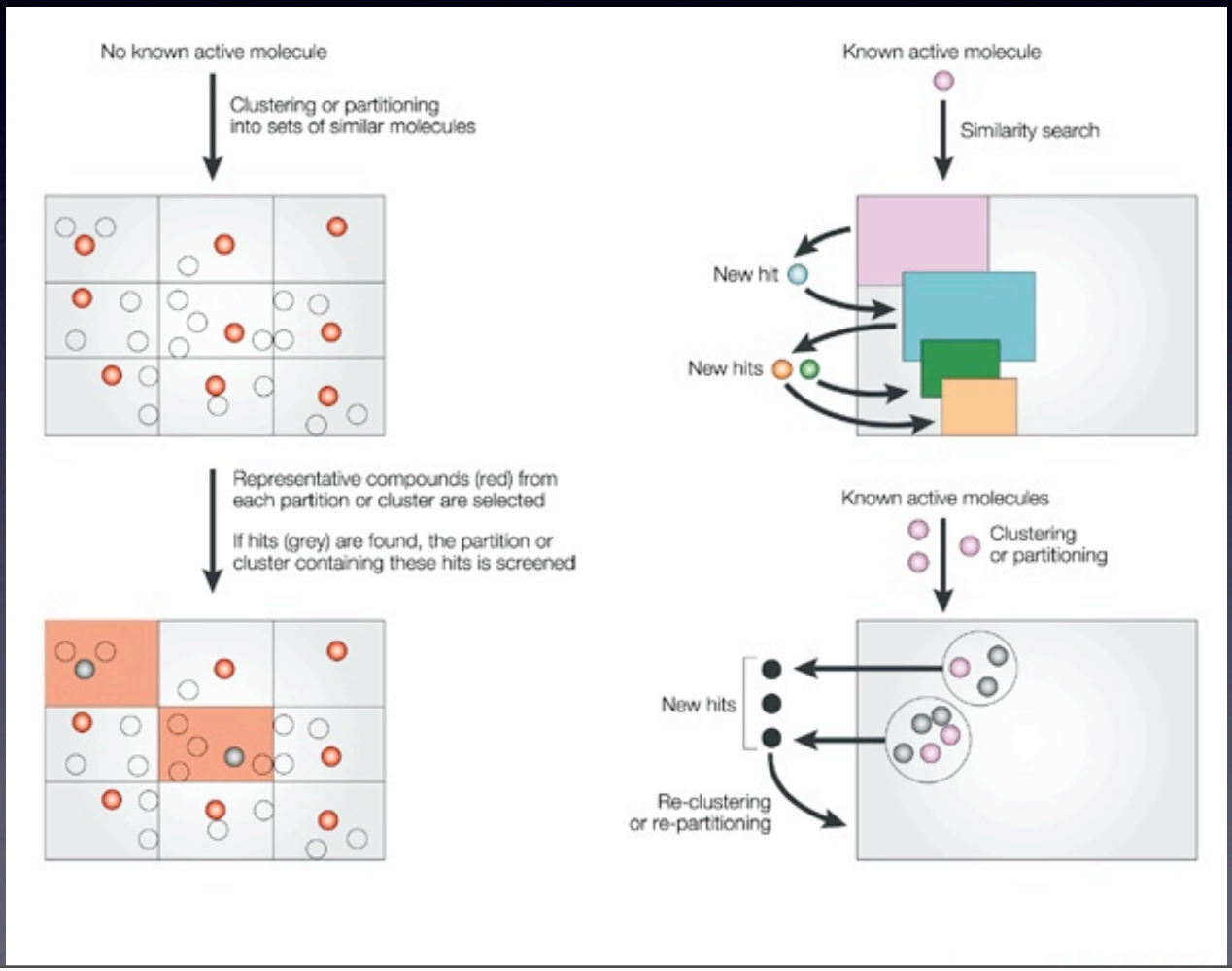
But....isradipine blocks both the Cav1.2 calcium channels found in smooth muscle and the brain Cav1.3 channel, limiting dosing.

A potent and selective Cav1.3 antagonist would offer a much more desirable clinical treatment strategy.



Human circulatory system, showing some of the major blood vessels. Arteries are color-coded red; veins are blue.

A collaborative effort has been mounted to use high throughput drug screening and medicinal chemistry to identify a better drug.



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- ✓ The aging and death of dopaminergic neurons appears to be a design fault, but we might be able to pharmacological redesign them to last.
- ✓ A clinical neuroprotection trial for PD is underway under the direction of Dr. Tanya Simuni at NU.

Acknowledgments:

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Thanks for your attention...